Lipogenesis and Carbohydrate Utilization

Effects of Glucose Concentration and Insulin in Rat Liver and Adipose Tissue

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We have recently reported that stock-fed normal rat adipose tissues are considerably more active in converting uniformly labeled C^{14} glucose into fatty acids in vitro than are the livers of the same animals.[1] The rates of glucose oxidation based on equal fresh weights are of comparable magnitude in both tissues. Alloxan diabetes abolished lipogenesis and depressed the carbohydrate oxidation in each case. Insulin restored both capacities to normal values and above depending on the length of administration.

The glucose concentration used in these experiments was 400 mg. per 100 cc., an arbitrary value which clearly does not match the physiological concentrations encountered in the normal and the insulin-treated animals. In an attempt to evaluate the relative participation of these tissues in carbohydrate utilization more precisely, we have investigated the effects of varying glucose levels on their lipogenic and oxidative activities.

EXPERIMENTAL PROCEDURES

The experiments were designed to use pooled tissues for each of the glucose concentrations tested. One hundred mg. of the adipose tissue, or liver, respectively, from six rats were used per flask. The medium contained uniformly labeled glucose in concentrations shown in figures 1, 2 and 3. The same incubation and analytical methods were used as in the earlier investigation.[1] Male Wistar rats weighing about 400 gms. were used. The insulin treated rats received 36 units of protamine zinc insulin over a period of 3 days so that a sustained hormonal effect was maintained during its administration. The rats gained weight rapidly during this time. The last injection was given 2 to 3 hours before the experiment, and blood sugar levels at sacrifice averaged about 50 mg. per 100 cc. The alloxan diabetic rats of that group in which hepatic oxidation was investigated, showed average blood glucose levels of 602 mg. per 100 cc., an average glucosuria of 11 gm. per day and a weight loss of 33 per cent from the time of the alloxan administration. The other group from which adipose tissue was taken showed corresponding values of 421 mg. per 100 cc., 9 gm., and 7 per cent.

EXPERIMENTAL OBSERVATIONS

Lipogenesis and Glucose Oxidation. Lipogenesis in normal liver was not detectable until a concentration of 400 mg. per 100 cc. of glucose was used. Adipose tissue, under identical circumstances, actively incorporated glucose C^{14} into its fatty acids at 50 mg. per 100 cc. and increased in this activity slightly at higher levels. Insulin treatment enabled the liver to commence lipogenesis at 50 mg. per 100 cc. and respond to higher glucose concentrations with marked increases in lipogenic capacity. Adipose tissues from such animals also had an activity elevated above normal, which exceeded that in the liver

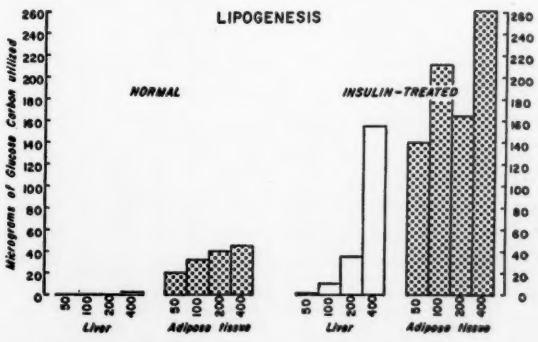

FIG. 1. Formation of fatty acids and carbon dioxide from radio glucose (50-1,600 mg. per 100 cc.). Values in micromoles per gm. of tissue per 3 hours.

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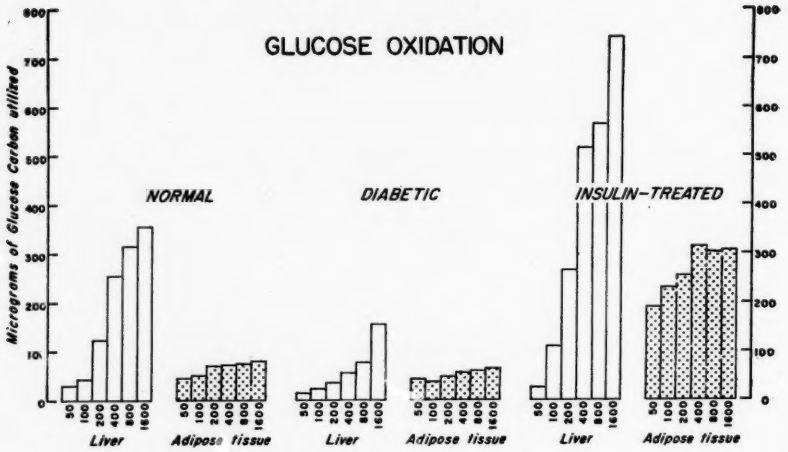

FIG. 2. See figure 1.

at all substrate levels except the highest studied. Lipogenesis in adipose tissue of the normal and hormonally stimulated animals did not respond to glucose concentrations as dramatically as did the process in the liver (figure 1). Preliminary experiments have indicated that both tissues from diabetic animals exhibit no detectable lipogenic activity at glucose levels up to 1,600 mg. per 100 cc.

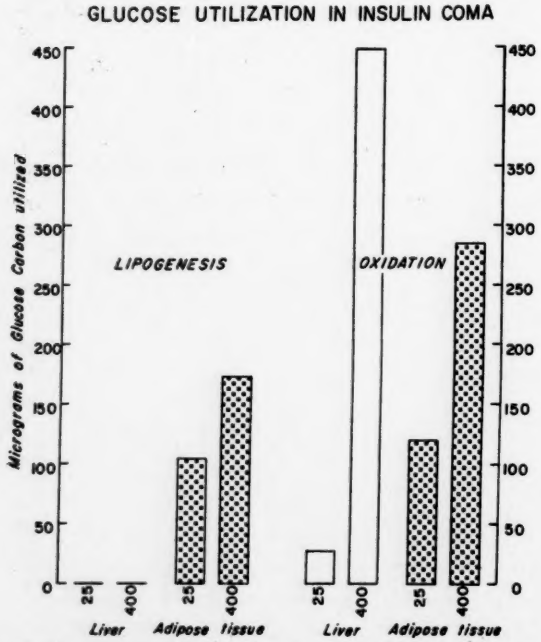

FIG. 3. Formation of fatty acids and carbon dioxide from radio glucose (25 and 400 mg. per 100 cc.). See figure 1.

Glucose oxidation (figure 2) was far more dependent on the exogenous concentration in normal liver than in adipose tissue. The latter appears to be functioning almost at a saturated substrate level at 50 mg. per 100 cc. Hepatic tissues from alloxan diabetic rats exhibited depressed oxidative rates which paralleled the normal values at corresponding sugar levels. Diabetic adipose tissue oxidation rates were not significantly different from normal, indicating a greater resistance of this tissue's oxidative function towards insulin deficiency. It should be pointed out, however, that these animals were not *maximally* diabetic. Unpublished investigations using the classical method of determining the glucose balance indicate that such diabetic rats are still able to utilize about half the amount of glucose utilized by normal animals.[2] In rats manifesting a more severe diabetes adipose tissue oxidation is also depressed.[1]

Insulin administered in moderate doses over a three day period enhanced oxidation in both tissues without distorting their characteristic response to the glucose concentrations. It is also of interest to note that adipose tissue carbohydrate oxidation as well as lipogenesis is greater than that in the liver at those glucose levels which correspond to the glycemic condition of the animal (figures 1 and 2).

Effects of Hypoglycemia. More acute hypoglycemia, averaging 25 mg. per 100 cc., was developed in rats given 40 units of protamine zinc insulin over a two- to four-hour period during which time food was withheld. When insulin reactions (unconsciousness or convulsions) were evident, the animals were sacrificed and their livers and adipose tissues incubated as before, using two glucose concentrations, 400 mg. per 100 cc. and 25 mg. per

100 cc.[3] The latter corresponded to the average blood sugar levels of these animals. Lipogenesis was absent in liver in both carbohydrate levels. Adipose tissue was clearly active in fat synthesis under these conditions and indeed was significantly more active than when taken from normal animals. Increasing the glucose level led to an enhanced oxidative response of the hepatic tissues, but the activity at the 25 mg. per 100 cc. glucose level (prevailing in vivo) was less than that in adipose tissue. The oxidative activity in adipose tissue at this level exceeded that found in the normal animals at 100 mg. per 100 cc., while, in the liver, no appreciable change from normal was seen.

DISCUSSION

Renold and co-workers have recently studied the biochemical sequence of events after insulin administration.[3] Their experiments suggested that insulin exerted immediate metabolic effects on the periphery only, while its effects on hepatic metabolism were more gradual, representing "either a different type of hormonal action or a metabolic adaption to the new demands created by the peripheral changes." Our data confirm the greater immediate extrahepatic action of insulin and suggest that adipose tissue as one element of the metabolic periphery may play an important part in the biochemical effects induced by the hormone. Furthermore, since adipose tissue suffers comparatively little diminution in its ability to utilize carbohydrates at falling blood sugar levels, it is tempting to think of it as a major site of metabolism during severe hypoglycemia. Earlier investigations have already indicated that adipose tissue may be of considerable importance in carbohydrate metabolism.[4, 5]

Our previous reports[1, 6] on the quantitative superiority of adipose tissue over liver as a site of fat formation in vitro have been amplified by these studies. They indicate even more strongly that the liver, under various conditions, may play only a supplementary role in lipogenesis. Adipose tissue, an organ of significant proportions in terms of total body weight, appears capable of major activities in the carbohydrate metabolism of the organism.

SUMMARY

Lipogenesis in isolated normal liver tissue of the rat was not detectable until a concentration of 400 mg. per 100 cc. of glucose was used. In contrast adipose tissue actively incorporated glucose C^{14} into its fatty acids at 50 mg. per 100 cc. Insulin administration led to lipogenesis by the liver at a glucose concentration of 50 mg. per 100 cc. and also stimulated lipogenesis at higher glucose levels both in liver and in adipose tissue. In general insulin did not enhance lipogenesis as much in adipose tissue as it did in liver. Diabetic tissues had no detectable lipogenic activity.

Glucose oxidation by adipose tissue appeared near maximum at glucose levels of 50 mg. per 100 cc. whereas in liver the oxidative removal of glucose increased with rising concentrations. Comparing glucose oxidation at prevailing blood levels of 100 mg. per 100 cc. for normals and 400 mg. per 100 cc. for alloxan diabetic rats, there was no significant difference between the two groups in either liver or adipose tissue. Insulin administration enhanced the oxidation of glucose in both tissues without distorting their characteristic responses to carbohydrate concentration.

In tissues from hypoglycemic rats, lipogenesis was absent in liver at glucose concentrations of 25 to 400 mg. per 100 cc. In contrast adipose tissue was clearly active in fat synthesis under these conditions and significantly more so than when taken from normal animals.

The data confirm the greater immediate extrahepatic action of insulin and suggest that adipose tissue may be an important site of the action of insulin.

SUMMARIO IN INTERLINGUA

Lipogenese e Utilisation de Hydratos de Carbon: Effectos de Concentration de Glucosa e Insulina in Histos Hepatic e Adipose de Rattos

Lipogenese in isolate normal histos hepatic de rattos non esseva detegibile usque un concentration de glucosa de 400 mg per 100 cm cubic esseva usate. In contrasto con isto, histos adipose incorporava glucosa a C^{14} activemente in su acidos grasse a un concentration de 50 mg per 100 cm cubic. Le administration de insulina resultava in lipogenese per le hepate a un concentration de glucosa de 50 mg per 100 cm cubic e etiam stimulava lipogenese a plus alte nivellos de glucosa in histos tanto hepatic como etiam adipose. In general, insulina non promoveva lipogenese tanto in histos adipose como illo lo faceva in histos hepatic. Histos diabetic non habeva un detegibile activitate lipogenic.

Le oxydation de glucosa per histos adipose pareva attinger su maximo in le vicinitate de nivellos de 50 mg per 100 cm cubic, durante que in histos hepatic le oxydation de glucosa accresceva con accrescente concentrationes. Le comparation del oxydation de glucosa in le presentia prevalente de nivellos sanguinee de 100 mg per 100 cm cubic in le caso de rattos normal e de 400 mg per 100 cm cubic in le caso de rattos con diabete alloxanogene monstrava nulle differentia significative inter

le duo gruppos in histos hepatic o in histos adipose. Le administration de insulina promoveva le oxydation de glucosa in ambe histos sin alterar lor responsas characteristic al concentration de hydrato de carbon.

In histos ab rattos hypoglycemic, lipogenese esseva absente in histos hepatic a concentrationes de glucosa ab 25 a 400 mg per 100 cm cubic. In contrasto con isto, histos adipose esseva clarmente active in le synthese de grassia sub le mentionate conditiones. Le grado de iste activitate esseva significativemente plus alte quando le histos adipose esseva prendite ab rattos normal.

Le datos citate confirma le plus grande immediate action extrahepatic de insulina; illos indica que histos adipose es possibilemente un importante sito del action de insulina.

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The Facets of Age

The problem of our senior citizens is becoming more important as the years go by. With each passing year the average life span grows longer, resulting in an ever-increasing population of aging or, perhaps we should say, aged persons.

Since 1940 the people sixty-five years and over have increased by nearly 50 per cent in the United States and now total 13,500,000. Between 1940 and 1950 the entire population of New York State increased 10 per cent, while our sixty-five and over group increased 39.3 per cent. One can not overestimate, therefore, the need for an active program aimed at alleviation of the many facets of the problems involved in the aging process. Such an attack must include not only a physiologic survey of the situation, but also and even more important the psychologic, social, and economic factors involved require attention and consideration.

Let us consider first of all, the thoughts and feelings of the aging:

In the involutional phase of the life cycle the ordinarily adequate adjustment between the instinctive force for self-preservation and race preservation breaks down, and a new physiologic adjustment and psychologic attitude are required. At this time of life the instinctive drive for race preservation abates, and the self-preservation drive reasserts itself more consciously. This results in an over-awareness of self and a lack of concern for others which at times occasions a most serious problem of adjustment. A change in philosophy is required. If this fails, the person becomes apprehensive and depressed.

He quite often distorts reality and exaggerates his limitations, so that a picture of neuroticism appears. External stimuli lose their zest, and anticipations which formerly gave rise to pleasure cause only a cynical attitude to develop which pervades his whole outlook on life.

Diminution of sensory acuity, especially of hearing and sight, so frequently found, interfere with social acceptability and ability to maintain effective comunication with the environment so that the individual tends to isolate himself. Someone has quite aptly applied the term, "social disarticulation," to this particular problem. Such partial isolation leads to misinterpretations and suspicions which, if allowed to go uncorrected, become distorted and result in increasing anxieties, fear, and discouragement. There are, of course, many other physical changes incident to the aging process, but time precludes the possibility of discussing all of them. Suffice it to say that physical changes constitute a real threat to older persons, but the important thing is the manner in which these changes are accepted.

H. A. Steckel, M.D., from an article
"Emotional Aspects of the Aging Process,"
New York State Journal of Medicine 55:3605-06, Dec. 15, 1955.

Diabetic Cataracts

A Review of Experimental Studies

John W. Patterson, M.D., Cleveland, Ohio*

The complications which follow prolonged diabetes are a major concern of the physician who is responsible for the care of diabetics. The prevention of these complications is hampered by our ignorance of their cause. The exact etiology of diabetes is not known, and the syndrome may result from a variety of metabolic defects which are usually undetermined.[1-5] Thus, it is difficult to study complications in relationship to the cause of diabetes. Furthermore, the time required for the development of complications following a diagnosis of diabetes may be long and the acquisition of knowledge therefore slow. As a result of these difficulties, it is not surprising that there are two opposite viewpoints regarding the relationship of the control of diabetes with insulin to the development of complications. Some believe that complications can be prevented by good control;[6] others believe that complications develop in spite of good control.[7] Studies with animals may provide clues to the mechanism by which diabetic complications are produced.

Permanent diabetes may be produced in animals by pancreatectomy[8] or by the injection of alloxan,[9, 10] dehydroascorbic acid and related compounds,[11-13] certain chelating agents,[14-16] or pituitary extracts.[17] Temporary diabetes may be produced by the continued injection of pituitary[18] or adrenal hormones.[19] The production of diabetes in animals is followed by the development of a variety of complications.[20] All of the complications associated with human diabetes are not readily reproduced. Cataracts, however, do appear in diabetic animals and are probably similar to the cataracts associated with juvenile diabetes in man.[21] Diabetic cataracts in rats develop through certain stages.[22] At first vacuoles are observed around the periphery of the lens. Later fine crystalline opacities develop centrally, and still later the lens suddenly becomes opaque. The last of these changes occurs over a period of 24 to 48 hours and is readily seen with the unaided eye. This can be used as an excellent indicator of a metabolic end point. By relating various experimental conditions to the appearance of this end point, it is possible to gain an insight into the factors that may cause this complication of diabetes. It is the purpose of this paper to relate some of the experimental work that has been done in relation to the development of cataracts. This will be done by considering three points: (1) the relationship of the severity of diabetes to cataracts; (2) diabetic factors that influence cataracts; and (3) evidence for a theory concerning the development of cataracts.

DIABETES AND CATARACTS

Following the production of diabetes with alloxan or dehydroascorbic acid, rats have hyperglycemia, glycosuria, polyuria, polydipsia, and polyphagia.[23] They fail to gain weight at a normal rate. Any one of these findings might be used as an index of the severity of the diabetes. However, the environment of the lens is most closely represented by the blood sugar level. Furthermore, the other changes are secondary as indicated by the fact that all of the other signs of diabetes may be reproduced by increasing the blood sugar level with another sugar such as galactose.[24] The nonfasting blood sugar is readily measured. Although the hyperglycemia varies slightly from week to week, the average of several determinations on a single rat or group of rats remains constant and serves as a useful measure of the environment of the lens.[23]

The time required for diabetic cataract formation bears an inverse relationship to hyperglycemia[23, 25] (figure 1). The relationship is described by the equation for a hyperbola. Thus, a minimum time is required for the maturation of a cataract regardless of the height of the blood sugar, and minimum elevation of blood sugar is required for the formation of cataracts. The minimal blood sugar is about 250 mg. per 100 cc. At this level the renal tubular reabsorption mechanism for glucose is saturated with a resultant loss of sugar in the urine and a tendency to ketosis and neoglucogenesis.

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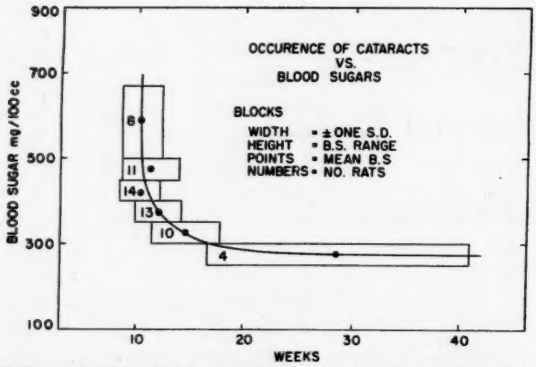

FIG. 1. Reprinted with permission of the "American Journal of Physiology."

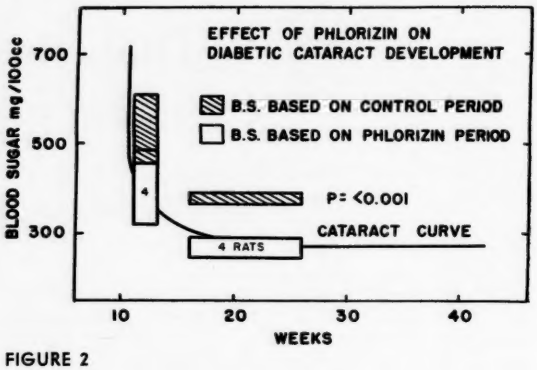

FIGURE 2

The relationship of the time required for the development of cataracts to the height of the blood sugar has led to the suggestion that the cataracts might be the result of one of the factors associated with diabetes. Hence, cataracts might be caused by the "toxic" effects of hyperglycemia or acidosis, by the destruction of proteins in neoglucogenesis, by the loss of an essential metabolite in the urine, or by the failure to absorb glucose in the absence of insulin. The fact that cataracts can be prevented by controlling these factors with insulin[25-28] supports the idea that one or more of them may play a mediating role in the production of cataracts.

DIABETIC FACTORS INFLUENCING CATARACTS

The possible mediating role of the various factors present in diabetes may be studied by changing the relative severity of the factors in diabetic animals and noting the effect on the time required for cataract formation. The administration of a high fat diet to diabetic rats is reported by Charalampous and Hegsted to eliminate glycosuria and prevent cataracts completely.[29] Fasting rats for a period of 40 hours each week lowers the blood sugar for the period of the fast and delays the formation of cataracts.[30] The administration of phlorizin to diabetic rats increases the loss of sugar through the kidney and hence lowers the blood sugar. The time required for cataract formation is significantly delayed in phlorizin-treated rats.[25] When the time required for cataract formation is related to the blood sugar level, the areas of cataract incidence fall on the expected cataract curve during the period of phlorizin administration. However, when related to the blood sugar values before phlorizin administration, the areas of cataract incidence do not fall on the expected cataract curve and thus demonstrate the delay produced by phlorizin (figure 2). Thus, the administration of a high fat diet, fasting, and the administration of phlorizin are beneficial in preventing cataracts. In each of these conditions, the blood sugar is lowered and the other metabolic changes of diabetes are aggravated. The general status as indicated by growth curves is not improved, and ketosis and neoglucogenesis are known to become worse in experiments of this type.[31, 32] Therefore, one is led to the conclusion that hyperglycemia must play a direct role in the production of diabetic cataracts.

If the high blood sugar level acts directly on the lens to produce cataracts, then the amount of sugar reaching the eye by the way of the blood stream should be of importance. This can be tested by altering the blood supply for one eye and using the second eye as a control.[33] Thus, in galactose-fed rats cataracts are first seen in the left eye in 56 per cent of the rats. However, when one of the carotid arteries is ligated and cut, 90 per cent of the cataracts are first observed on the side with the better blood supply and hence the better supply of galactose. In diabetic rats, however, the occurrence of cataracts is unrelated to the blood supply (figure 3). Since diabetic cataracts develop more slowly than galactose cataracts, the results might be explained on the basis of the development of collateral circulation. However, this is unlikely since rats with unilateral carotid ligation in which galactose feeding is delayed still develop cataracts preferentially on the side with the greater blood supply (figure 3). Since carotid ligation in normal rats does not cause cataracts and since carotid ligation in diabetic rats does not affect the side on which cataracts are first observed, one is led to the conclusion that cataracts in galactose-fed rats are related to the amount of blood and hence the amount of galactose reaching the eye. The failure of carotid ligation to influence cataract formation in diabetic rats leads one to question the hypothesis that hyperglycemia is directly responsible for the production of diabetic cataracts.

If diabetic cataracts are not the result of high levels of

EFFECT OF BLOOD SUPPLY ON DEVELOPMENT OF CATARACTS

TREATMENT	NO. RATS	PER CENT OF CATARACTS FIRST SEEN ON SIDE WITH BETTER BLOOD SUPPLY. (50 / 100)
35% GALACTOSE	16	
CAROTID CUT	16	
DIABETES	23	
CAROTID CUT	15	
CAROTID CUT 35% GALACTOSE AFTER 40 DAYS	7	

FIGURE 3

glucose working on the eye, then the role of hyperglycemia in producing cataracts needs to be re-evaluated. Hyperglycemia has been implicated as a factor in the production of cataracts because of the direct relationship between the height of the blood sugar and the rate at which cataracts appear and because cataracts can be prevented by lowering the blood sugar with phlorizin, a high fat diet, or fasting. The first point might be explained by assuming that some factor which parallels hyperglycemia is directly responsible for cataracts. A lack of insulin could be such a factor. If this is accepted as a possibility, then the second point may also be explained. If a lack of insulin produces cataracts, then cataracts are probably the result of an inability to obtain energy by utilizing glucose. Lowering the blood sugar with resulting ketosis would supply an alternate source of energy for the lens. If this raises the total energy supply above the "critical level," cataracts would be prevented (figure 4). Furthermore, if diabetic cataracts are the result of the inability of glucose, in the absence of insulin, to supply energy for the lens, the development

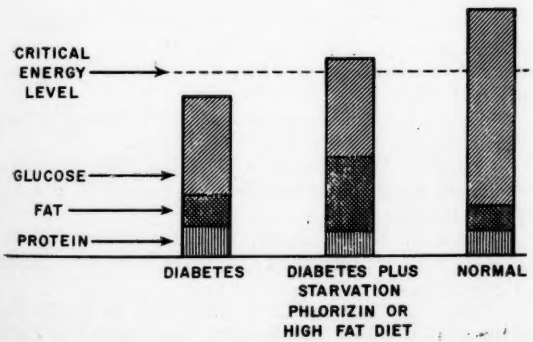

FIG. 4. Diagram of possible sources of energy for lens.

would be independent of the blood supply. Thus, the known facts can be explained by a mechanism that does not involve a direct action of hyperglycemia in the production of cataracts.

EVIDENCE FOR A THEORY

The following mechanism is proposed for the development of diabetic cataracts. In the absence of insulin, the uptake of glucose by the lens is impaired. Since the lens depends on glucose for a major portion of its energy, the total available energy is lowered beyond the critical point that is necessary for maintaining transparency. The lens is also dependent on the constituents in the blood for alternate sources of energy. Under ordinary circumstances, the quantity of these substances is determined by the other organs, notably the liver, and the amount in the blood is inadequate to supply the lens with energy. A decrease in available energy could produce cataracts by stopping the synthesis of glutathione,[34-38] enzymes,[39, 40] proteins,[41, 42] or other structural compounds,[43] or by blocking the maintenance of a water[44] and electrolyte balance.[45, 46] This hypothesis is supported by studies on glucose uptake on isolated lenses and by studies with diets that supply energy-yielding substances other than glucose.

Isolated rat lenses, which are washed and incubated at 37° in Tyrode's solution containing 100 mg. glucose per 100 cc., remove the glucose from the medium at a constant rate for a period of several hours.[47] Lenses obtained from rats with diabetes of one week's duration have an uptake of glucose that is less than half the normal value. This is a significant impairment in the uptake of glucose by the lenses of diabetic rats (figure 5). Ross[48] has reported that insulin will increase the uptake of glucose in isolated decapsulated lenses from normal rabbits. This has not been studied with rat lenses. Fasting the animals for a period of 16 hours prior to the removal of the eyes does not alter the glucose uptake of the normal or diabetic lenses. Thus, the beneficial effects of fasting on the prevention of cataracts may not be related to glucose uptake and may be associated with the production of ketone bodies as an alternate source of energy.

A diet consisting of 50 per cent fructose, 25 per cent casein and 25 per cent fat that is fortified with vitamins and minerals provides energy-yielding substances that can be utilized in the absence of insulin.[49] When this diet is fed to animals most of the fructose is rapidly converted to glucose[50] and the blood sugar level of fructose is between 10 and 20 mg. per 100 cc. of blood. Unlike other high fat diets, however, the hyperglycemia of diabetes is not lowered. The use of fructose as a source of carbohydrate makes it possible to maintain high blood sugar levels for an indefinite period. The fact that this diet also

EFFECT OF DIABETES ON GLUCOSE UPTAKE OF RAT LENS.

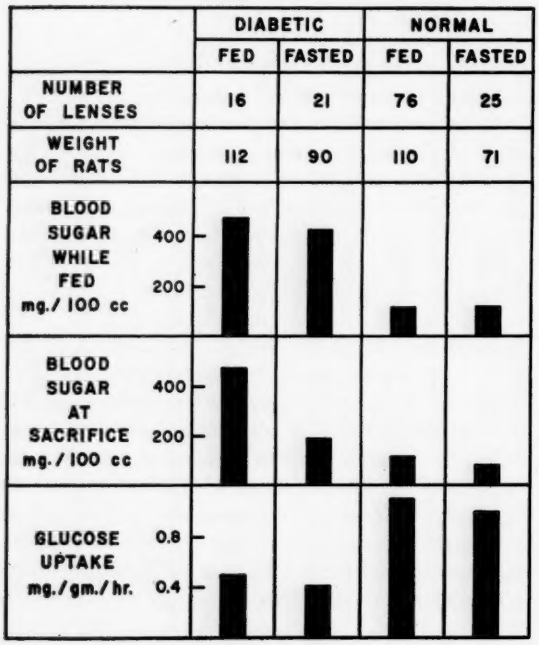

FIGURE 5

prevents the development of cataracts definitely rules out hyperglycemia as a direct mediator in the production of cataracts and demonstrates that the incidence of cataracts can be reduced with the special fructose-high fat diet to 20 per cent of that with a chow diet (figure 6).

EFFECT OF HIGH FRUCTOSE, FAT AND CASEIN DIET ON DEVELOPMENT OF DIABETIC CATARACTS.

DIET	NO. RATS	AVE. WT. gm.	BLOOD SUGAR mg./100 cc. CONTROL	BLOOD SUGAR mg./100 cc. ON DIET	PER CENT WITH CATARACTS AT 150 DAYS
SPECIAL	10	125	450	448	P <0.001
CHOW	10	129	490	475	

FIGURE 6

Growth curves of rats on this diet are also different from those of rats on other high fat diets. On a sucrose-high fat diet rats do not gain weight over a period of three months.[29] However, on a fructose-high fat diet the growth rate is accelerated. Thus, rats with apparently severe diabetes grow at a rate that would be expected for mild diabetes. It would appear that a diet which provides substances that do not require insulin for utilization has a beneficial effect on many tissues of the body.

SUMMARY

This study of one of the complications of diabetes provides evidence indicating that at least one tissue in the body degenerates in uncontrolled diabetes because it is unable to absorb glucose and because alternate nutrient substances are not available in adequate quantities. The provision of a diet containing substances that do not require insulin for utilization prevents this tissue degeneration.

SUMMARIO IN INTERLINGUA

Cataractas Diabetic: Un Revista de Studios Experimental

Iste studio de un del complicationes de diabete demonstra que al minus un del histos corporee se degenera in nonsubjugate diabete proque illo es incapace a absorber glucosa e proque substituibile substantias nutriente non es disponibile in adequate quantitates. Iste degeneration de histos es evitabile per le provision de un dieta que contine substantias que non require insulina pro lor utilisation.

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Islet Pathology in Diabetes

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The title assigned me, "Islet Pathology in Diabetes," implies that lesions of the islets of Langerhans may be responsible for the diabetic state. Although this concept has merit in some types of the disease, in others direct evidence to support it is lacking. In a significant number of adult diabetics, present-day methods of examining the pancreas fail to reveal either faulty islet structure or function. I will present my discussion in three parts.

The first two will consist of a brief review of the histology of the normal islets of Langerhans and their pathologic changes in experimental animals in which diabetes has been produced. Finally morphology of the islets in diabetic man will be reviewed.

The remarkable collections of highly specialized endocrine cells scattered throughout the pancreas and constituting an organ within an organ are aptly named the islets of Langerhans after the individual who first described them in the text of his doctoral thesis. Since the discovery of von Mering and Minkowski in 1889 that removal of the pancreas would cause diabetes in experimental animals, attention has been focused on this organ. The first description of pathologic lesions of the islets in diabetic man correlating clinical and pathologic findings is that of Eugene L. Opie,[1] the first of my three predecessors occupying the Mallinckrodt Chair of Pathology at Washington University Medical School. Also one of the best descriptions of normal islets in man is that of Opie,[2] and much of what we know today is in his account written over fifty years ago.

The weight of the normal pancreas in adult man is 50 to 75 gm. From their careful mensurational studies, Maclean and Ogilvie,[3] have recently reported that the islet tissue accounts for approximately 1/50 of the total weight of the organ, or a little over 1 gm. The distribution of the islets varies throughout the organ. They occur with increasing frequency as one progresses from its head to its tail. The largest are nearest ducts in the centers of the pancreatic lobules.

A number of special staining reactions that differentiate the various types of islet cells have been devised. The series of neutral stains introduced by Lane and modified by Bensley, Bowie and others were popular until the last war. With those stains it is apparent that about four or five beta cells are present for every alpha cell. In man, the alpha cells are distributed rather irregularly throughout the islet, but in some species they characteristically occupy special portions of each. In the rat and guinea pig, alpha cells are found at the peripheries, in the dog they occur more frequently in the centers, and in some of the avian species, such as the duck, whole islets apparently composed of nothing but alpha cells may be found.

Some years after the introduction of the neutral stains, trichrome procedures using azocarmine, aniline blue and hematoxylin became popular. By this procedure granules in the alpha cells appear deep red, those in the beta cells pale pink, and in addition a third type of cell contains granules that stain with aniline blue. The latter are delta cells, which occur only in small numbers, amounting to probably less than 1 per cent of the total cells in the islets. The function of D cells is a matter of sheer speculation. Aniline blue also serves to stain the delicate basement membranes supporting the sinusoids, thus affording still another advantage to these trichrome technics. But many of these stains just described, and others not even mentioned, have in most laboratories been displaced currently by the technics developed by Gomori[4] in Chicago. His contributions to this field have been outstanding in recent years. Two of the methods he has developed are extremely popular. The first employs a chromium salt of hematoxylin, which stains the granules in the beta cells a beautiful navy blue, and phloxin, which colors those in the alpha cells rosy red. Delta cells are not demonstrated by this technic and are indistinguishable from alpha cells. This method of Gomori's is exceedingly useful for rapid and ready differentiation of the two most numerous types of islet cells in man, alpha and beta.

Gomori has also devised an important method for demonstrating even more selectively the granules in the beta cells. His aldehyde-fuchsin technic has been modi-

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fied by Wilson in Toronto, who first mordants the sections in potassium permanganate and counterstains with Light Green. Granules in beta cells appear intensely purple and those in alpha cells green. Under the microscope, granules stained in this manner can be resolved individually. This technic far surpasses any other available method for their positive identification. Beta granules are considered to represent insulin or a precursor thereof, both in animals and man.

Variations in islet morphology occur with age. Bencosme[5] found that in the initially formed islets of the embryo rabbit, differentiation of alpha and beta cells had already occurred. As the islets grow, alpha cells produce only more alpha cells and beta cells only more beta cells. Available evidence fails to support the hypothesis that alpha cells represent transitions between beta and acinar cells, as once proposed. At birth and for a few months afterwards in the infant, the proportion of alpha to beta cells is greater than in the adult. But Maclean and Ogilvie[3] in their study did not find any appreciable change with age in the *total* number of islets in the pancreas or in the number of islets per mg. of pancreas, from 10 to 80 years.

There is little doubt that electron microscopy, affording much higher magnifications than we have achieved before in studies of islet cells, will prove a valuable aid in clarifying some of the problems connected with the histology and pathology of islets. Dr. Paul Lacy[6] has embarked upon an extensive program of the histochemistry and electron microscopy of the islet of Langerhans in man and experimental animals. He has succeeded already in obtaining electron micrographs of alpha, beta, and C cells in the normal guinea pig. His technic involves the preparation not only of ultra-thin sections for electron microscopy but also of comparably thin sections for light microscopy. Thereby a correlation between the familiar appearances with the light microscope may be made with the new in electron micrographs. Figure 1 is an electron micrograph kindly provided by Dr. Lacy. The cells with the largest and darkest granules are beta cells, and those with the somewhat sparser and smaller granules are alpha cells. Those without granules are C cells.

Figure 2 provides a contrast side by side of all three types of cells. Below is an alpha cell, recognizable by the following features: The granules are dark and, although they vary in size, on the average they are somewhat smaller than those in the beta cell above and the nucleus is lighter. In the beta cell we see not only granules but mitochondria, and their differentiation is difficult as contrasted with the alpha cell. The nucleus of the C cell is not included; its cytoplasm contains only a few mitochondria but granules are absent.

Summing up our knowledge of the normal morphology of islets in man, we can say that they represent probably about 1/50 of the weight of the entire pancreas; they are more numerous in the tail than in the head of the organ; they are most frequently found in conjunction with ducts near the centers of the pancreatic lobules, and are composed of a variety of cell types, of which the most populous are the alpha and the beta. Differentiation of cell types may be accomplished by a variety of tinctorial procedures and by electron microscopy. Beta cells outnumber alphas in the ratio of 4 or 5 betas to 1 alpha in the adult, but perhaps only 2 to 3 in the newborn. Evidence is available which conclusively establishes that beta granules represent insulin or a precursor thereof. I shall say little about the function of alpha cells. Many of you are familiar with the available evidence concerning the secretion of glucagon by alpha cells, but as data relating abnormal states of the alpha cells to diabetes are sketchy at best, I shall not review this subject.

THE ISLETS OF LANGERHANS IN EXPERIMENTAL DIABETES

All available methods for producing diabetes in the experimental animal are characterized by islet damage. The methods may be grouped under the general headings of surgical (pancreatectomy, total or subtotal), toxic (injection of alloxan or related compounds), hormonal (imbalances produced by injection of anterior pituitary extracts, ACTH or growth hormone, cortisone, or thyroxin fed to the partially depancreatized animal) and finally, metabolic. The latter term refers to the classic experiments of Lukens,[7] who produced diabetes in cats by repeated intraperitoneal injections of 20 per cent glucose in saline and characterized by vacuolar change of the beta cells.

Total pancreatectomy, of course, does not leave any islets to study, but subtotal pancreatectomy in common with the diabetes which follows hormonal imbalances and administration of excessive amounts of glucose is characterized by extensive degeneration of beta cells. Vacuolation follows or accompanies degranulation in a progressive manner until the entire cytoplasm of every beta cell is reduced to an apparently empty sac. This type of degeneration was regarded as hydropic until the investigations of Toreson.[8] He demonstrated that most, if not all, forms of so-called hydropic vacuolation of beta and duct cells in experimental and clinical diabetes were actually glycogenic, for the vacuoles contain

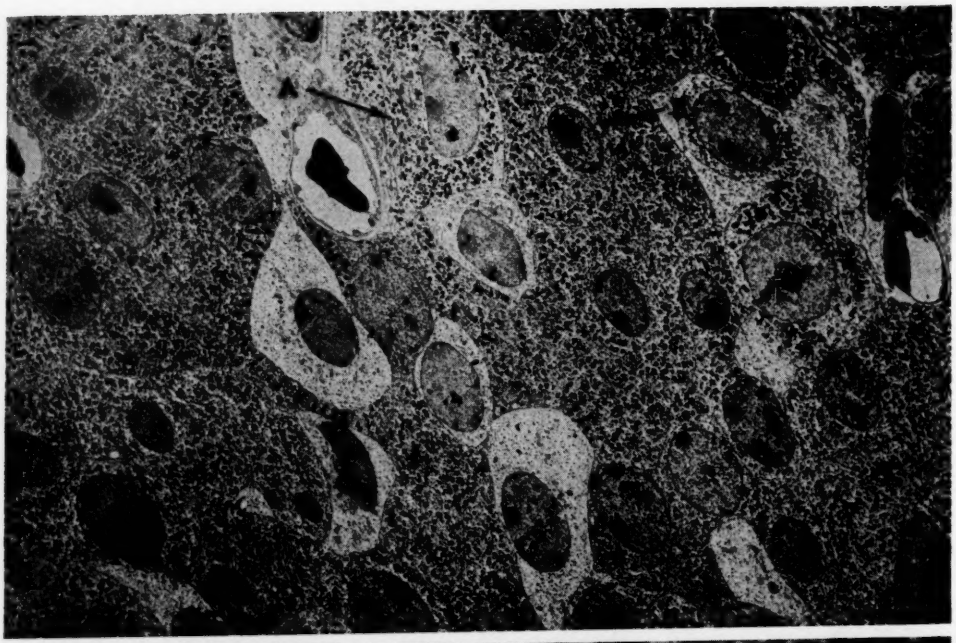

FIG. 1

(Legend at right)

FIG. 2

(Legend at right)

abundant, abnormal deposits of stainable glycogen.

Whether experimental diabetes follows hormonal imbalances, subtotal pancreatectomy or infusions of glucose, it appears that the experimental procedure induces a state in which the available amount of insulin is not adequate to meet the demand. This state of affairs is achieved in subtotal pancreatectomy, of course, by reducing the amount of insulin-producing tissue and in the hormonal experiments by increasing the demand for insulin from the normal amount of tissue present. Production of diabetes by injection of alloxan or related compounds is, however, the result of a selective necrotic action of the drug upon the beta cells, thus destroying them but sparing the other cell types.

FIG. 1. Electron micrograph of an islet of Langerhans of a guinea pig showing alpha, beta and C cells at low magnification. Two types of granular cells are apparent. The alpha cells (A) appear along the capillaries as light granular cells containing numerous granules, a small amount of ergastoplasm and a light gray nucleus. The more numerous beta cells (B) appear darker and contain scattered granules, abundant ergastoplasm and a dark gray nucleus. The C cells (C) appear pale gray and contain no granules or a few indistinct ones, few mitochondria and a small amount of ergastoplasm. A portion of an acinar cell containing zymogen granules is present in the lower right corner. Magnification 2,300 x.

FIG. 2. Electron micrograph of an alpha, beta and a portion of a C cell of the guinea pig. The beta cell is the uppermost nucleated cell and beneath it is an alpha cell. A portion of the cytoplasm of a C cell appears to the right of these and it is bounded above by a cytoplasmic projection from another alpha cell. The beta cell contains fewer and slightly larger granules, more abundant ergastoplasm, and a darker nucleus than the alpha cell. The C cell cytoplasm is devoid of granules. Magnification 13,500 x.

Available evidence from all varieties of animal experiments indicates that the severity of the diabetes, the amount of extractable insulin present in the animal's pancreas and the numbers of beta cell granules can all be correlated. The fewer the numbers of beta granules due to either cellular degeneration or necrosis, the less the amount of extractable insulin in these pancreases and the more severe will be the diabetic state of the animal. It results from the induction of either an absolute or relative deficiency of insulin. As far as I am aware, diabetes in an experimental animal has not yet been produced without loss of extractable insulin in the pancreas accompanied by degranulation of beta cells. Spontaneous canine diabetes is similarly characterized.[8] Yet diabetes exists in man in the presence of rather abundant amounts of insulin in the pancreas, and appreciable numbers of beta granules.

ISLET PATHOLOGY IN DIABETES OF MAN

As islets are invisible to the naked eye, little can be said about their gross pathology in diabetes. In some very obese diabetics, the normally pink parenchyma of the organ may be largely replaced and infiltrated by yellow adipose tissue. But many obese exhibit fatty infiltration of the pancreas at autopsy without ever having had diabetes and, of course, many diabetic patients do not have fatty infiltration of the pancreas. According to several published series, in approximately 30 per cent of pancreases of diabetics, severe fatty infiltration had developed.

Microscopically, degeneration accompanied by degranulation of the beta cells is found, according to various authors, in 5 to 15 per cent of adult diabetics. In a recent review of 100 consecutive cases of diabetes in our files at Washington University, this type of lesion was more frequent in acute diabetes of short duration. Inflammatory conditions are a rare cause of diabetes, constituting less than 1 per cent of all cases. It is reasonable to suppose, although not proven, that these various types of degenerations may represent the initial phase of a progressive lesion that may later reach frank hyalinization and/or fibrosis.

Hyalinization, with or without fibrosis, is probably the most clear-cut lesion present in diabetics examined at autopsy. Basement membrane thickening may precede hyalinization which affects a significant number of islets in 25 to 40 per cent of adult diabetics. Nuclei of beta cells in such islets may be shrunken and dark, while granules, although present, may be reduced in number. The site of hyalin deposition is usually between the lumina of the islet sinusoids and the beta cells. This type of lesion is more commonly associated with older diabetics or cases of mild diabetes of long duration. The amount of hyalin increases with age in both diabetics and nondiabetics, and is reported to occur in minor degree in up to 25 or 30 per cent of nondiabetics over the age of 50 years. Nevertheless, at any given age the extent and severity of hyalinization of islets is greater in adult diabetics than in nondiabetic adults. Unfortunately, the presence of hyalin in many nondiabetics in the upper age groups prevents this lesion from being regarded as pathognomonic of diabetes. Wilson,[9] in Professor Best's laboratory in Toronto, has recently been studying the relation of fatty degeneration of the islets to hyaline deposition and has stained frozen sections of hyalinized islets from diabetics for fat. He has found that the hyalin itself contains abundant amounts of stainable lipid. Rims of nonhyalinized islet tissue at the periphery of these islets are sometimes

fatty, even though not containing hyalin, suggesting that perhaps the fatty degeneration precedes and disposes to hyalinization. Wilson has also demonstrated rather large branches of the pancreatic artery completely occluded by fat in diabetics' pancreases. The significance of these lesions is not apparent at present, and we are awaiting with great interest further results of this study.

Although pathologic lesions of a variety of types are sometimes present in islets of adult diabetics, in a number of cases all or even any of these lesions may be absent, and any or all of these lesions may be present in nondiabetics. These facts have persuaded many investigators that the answer to the search for better correlation of clinical with morphologic findings may be found in quantitative studies. A number have now been completed, some very recently. In Toronto, Dr. Wrenshall and I[10, 11] attempted a correlation of the amounts of extractable insulin with the abundance of beta granules. Our results indicate that the pancreases of many diabetics contain not only less insulin but also fewer islets and scantier beta cell granules than those of nondiabetics. Although considerable overlap exists between the two groups, statistically there is no question that the average amount of insulin and the average numbers of beta granules in the diabetic pancreases are significantly less than in the nondiabetic. Furthermore, the correlation of the amounts of extractable insulin with the numbers of beta cell granules in both series established beyond any statistical doubt a one-to-one relationship between insulin and the beta granules. The slope of the correlation lines in the two series was significantly different. In the case of the diabetics, insulin is represented by fewer granules than in the case of the nondiabetics. Possibly more of the granules in the beta cells of the diabetics than in nondiabetics were so small they could not be resolved with the light microscope, so that those that could be seen would appear to represent more insulin than in the nondiabetics where perhaps most of the granules were visible with light microscopy. Very likely the validity of this explanation can be established or refuted by means of electron microscopy. Dr. Lacy may attempt such an investigation at least in animals, if not in man.

In their recently published report on quantitative estimation of the pancreatic islet tissue in diabetic subjects, Maclean and Ogilvie[8] established rather clearly that the proportion of alpha to beta cells increased so that one alpha cell was present to every 2.3 beta cells instead of 4.6 as in the nondiabetics. The altered ratio resulted from greater proportionate loss of beta than alpha cells in the diabetics. Although the total amount of islet tissue was less in the diabetics, there was a tendency for an increase in the mean size of individual islets with increasing age in diabetics, but not in nondiabetics. Maclean and Ogilvie's mensurational studies have supported earlier observations of Opie and others that columnar hyperplasia may frequently be encountered in the diabetic individual. Perhaps this change represents a compensatory phenomenon.

All investigators agree that in juvenile diabetics the picture is entirely different. Amounts of extractable insulin and beta cell granules are very low, if not entirely absent, in most of these cases that have been investigated at autopsy. In Maclean and Ogilvie's series the calculated weight of beta cells in the diabetics was clearly lowest and approached zero in the youngest individuals in their series, and increased linearly with age. Thus the extent of beta cell degranulation decreases and the amount of hyalin deposits in islets increases with the age of the diabetic, as emphasized by Bell.[12]

Before summing up I would like to say a word or two about diabetes associated with hemochromatosis. Although this special type of diabetic is rare (less than 2 per cent of all individuals suffering with the disease) the pancreas exhibits interesting and perhaps important features. Deposits of stainable iron are present throughout all portions of the gland, acinar, duct and islet tissue in these cases. In recent studies of pancreases of hemochromatotic individuals at Washington University, we became impressed with two features which appear unique in this type of diabetes. Firstly, we have not been able to demonstrate iron pigment in a single recognizable alpha cell, although it is found in nearly every beta cell. Secondly, the amount of iron deposited in any beta cell appears inversely related to the numbers of its granules. Dr. Malcolm McGavran in our department is completing this investigation. Thus far, his results indicate that alpha cells present in the islets of these individuals are fewer in number than in pancreases of nonpigmented diabetics. The ratio of alpha to beta cells is increased in the common types of adult diabetes. These results present you only with a few new facts. We hope that at the conclusion of these investigations some clue to the mysteries of hemochromatosis may have emerged.

SUMMARY

Extensive quantitative and qualitative investigations of the morphology of the islets of Langerhans in man and in animals have established many criteria for their normality. Advances in tinctorial technics largely contributed by Gomori have confirmed and extended the earlier investigations of Opie, Lane, Bensley and others. Further advances in the morphology of the pancreatic

islets will probably come from application of electron microscopic technics. Some early results in this field obtained by Dr. Paul Lacy have been briefly presented.

Diabetes can be produced in experimental animals by a variety of methods including surgical, hormonal, or toxic. All result in destruction or removal of either beta cells or their granules with an accompanying decrease in amounts of extractable insulin. As far as I am aware, there is no method of producing in an animal experimental diabetes which is associated with a significant amount of insulin in the pancreas at autopsy or significant numbers of granules in its beta cells. This fact is in sharp contradistinction to the universally conceded failure to demonstrate significant pathologic lesions in the islets of probably a quarter of all adult diabetics coming to autopsy. Although insulin and beta cell granules in the pancreases of adult diabetics are significantly less than in nondiabetics, there is considerable overlap between the two groups, and many diabetics, unlike the experimental animals, contain in their pancreases appreciable amounts of both extractable insulin and beta cell granules. Juvenile diabetics differ, however, in that almost without exception little or no insulin and beta cell granules can be found in their islets. Demonstrable lesions in the islets of adult diabetics include various degenerative changes of the beta cells accompanied by degranulation, basement-membrane reduplication, hyalinization and fibrosis. At certain stages at least, the hyalinization is accompanied, if not preceded by, rather striking degrees of fatty degeneration. It is possible that all these various abnormalities represent stages in the progression of a single type of lesion. Indeed, microscopic studies irresistibly suggest that the degenerative cytologic changes precede the structural alterations of hyalin or fibrous change. Recent mensurational evidence substantiates the impressions of earlier observers that in some diabetics' pancreases, islets may regenerate, a reassuring note to those who have not given up searching for factors that control islet hyperplasia, thus offering hope for discovering a cure of the disease for at least some individuals. Unique features of the unusual type of diabetes encountered in individuals suffering from hemochromatosis have been described.

Unless electron microscopy, histochemistry, or some other new approach reveals hitherto unsuspected abnormalities of islets in some 25 per cent of adult diabetics, we cannot blame the islets of these individuals for their disease. In their cases, extrapancreatic factors may be more important in correlating clinical and pathologic findings. I have said nothing of the role of the pituitary or the adrenal, etc., in the possible pathogenesis and etiology of diabetes in man, as such a discussion lies outside the scope of my assigned title. The consensus of opinion concerning the importance of the diabetogenic role of the pancreas *versus* extrapancreatic factors has swung from one extreme to the other over the years. Like many other scientific controversies, it is not at all unlikely that the truth lies somewhere between.

SUMMARIO IN INTERLINGUA

Pathologia del Insulas de Langerhans in Diabete

Extense investigationes quantitative e qualitative del morphologia del insulas de Langerhans in homines e animales ha establite multe criterios pro lor normalitate. Progressos technic de coloration, principalmente contribuite per Gomori, ha confirmate e extendite le investigationes anterior de Opie, Lane, Bensley, e alteros. Progressos additional in le studio del morphologia del insulas pancreatic va probabilemente resultar del application de technicas de microscopia electronic. Certe resultatos jam obtenite in iste campo per Dr. Paul Lacy es brevemente delineate.

Diabete pote esser producite in animales experimental per un varietate de methodos de genere chirurgic, hormonal, e toxic. Omne iste methodos resulta in le destruction o ablation de cellulas beta o de lor granulos, con un accompaniante reduction in le quantitate del extrahibile insulina. Intra le limites de mi cognoscentias, il existe nulle methodo de producer in animales experimental un diabete que es associate con significative quantitates de insulina intrapancreatic observabile al autopsia o con significative numeros de granulos in le cellulas beta del pancreas. Iste facto contrasta acutemente con le admission universal que nulle significative lesiones pathologic es demonstrabile in le insulas de Langerhans de probabilemente un quarto de omne diabeticos adulte qui es presentate al autopsia. Ben que insulina e granulos de cellulas beta in le pancreas de diabeticos adulte es significativemente reducite in comparation con nondiabeticos, il ha probabilemente un considerabile area de coincidentia inter le duo gruppos, e multe diabeticos—in contrasto con animales experimental—porta in lor pancreas appreciabile quantitates de extrahibile insulina e de granulos de cellulas beta. Diabeticos juvenil, il es ver, devia ab iste regula in tanto que con pauc exceptiones parve o nulle amontas de insulina e de granulos de cellulas beta es trovabile in lor insulas de Langerhans. Le demonstrabile lesiones in le insulas de Langerhans de adultos include varie alterationes degenerative del cellulas beta accompaniate de disgranulation e de reduplication, hyalinisation, e fibrosis del membrana basal. A certe stadios le hyalinisation es accompaniate, si non precedite, per satis frap-

pante grados de degeneration adipose. Il es possibile que omne iste anormalitates representa stadios in le progression de un sol typo de lesion. De facto, studios microscopic suggere con alte grados de probabilitate que le degenerative alterationes cytologic precede le alterationes structural de hyalina o le alteration fibrose. Mesurationes obtenite in recente studios reinfortia le impression de observatores anterior que le insulas del pancreas de certe diabeticos pote regenerar se. In iste situation il ha aspectos que incoragia le investigatores qui non ha abandonate lor spero de trovar factores capace a regular le hyperplasia del insulas de Langerhans e de aperir assi le via verso le possibile discoperta de un cura del morbo in al minus certe gruppos de casos. Es describite aspectos unic del inusual typo de diabete que es trovate in individuos suffrente de hemochromatosis.

Si le microscopia electronic, le histochimia, o alicun altere methodo de investigation non revela usque nunc noncognoscite anormalitates del insulas de Langerhans de circa 25 pro cento del diabeticos adulte, on non pote attribuer le morbo de ille individuos a lor insulas de Langerhans. In tal casos, factores extrapancreatic es possibilemente plus importante pro le correlation del constatationes clinic e pathologic. Io ha omittite omne referentia al rolo del glandulas pituitari o adrenal, etc., in le possibile pathogenese e etiologia de diabete in homines, proque le discussion de tal questiones excede le limites del thema assignate a me. Le opiniones prevalente in re le importantia del rolo diabetogenic del pancreas in comparation con le rolo de factores extrapancreatic ha oscillate inter le duo extremos in le curso del annos. Il non es del toto improbabile que hic, como in multe altere controversias scientific, le veritate se trova alicubi in le region intermediari.

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The Metabolic Potential of Adipose Tissue

For many years adipose tissue was considered to be only a storage depot for fat, the very designation "depot" implying that the tissue played no primary role in metabolism. However, the evidence collected during the past twenty years has stressed the metabolic potential of this widely distributed tissue.

Many publications have appeared on the respiratory characteristics of adipose tissue. They might be summarized by saying that the oxygen consumption of the tissue is inversely proportional to fat content and varies directly with the nitrogen content of the "depot." The level of metabolic activity is determined by dietary, neural and endocrine factors. The metabolic service of adipose tissue to the body economy would appear to be two-fold. It accumulates the triglycerides from the diet and liver that are carried by the blood stream to the depots and stored there until mobilized by as yet unknown mechanisms. The other, more important function to the body may be the conversion of blood glucose to fatty acids that are stored as triglycerides for future use. Recent research indicates that the latter function may be of great importance to an understanding of the biochemical basis for obesity.

From "Diet and Lipogenesis in Adipose Tissue"
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Effect of Strain Differences on Alloxan Diabetes in Albino Rats

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Studies in this laboratory on the details of the alloxan reaction in albino rats of Wistar parentage have revealed a number of features hitherto not reported in this or other species of experimental animal.[1, 2, 3] These features include:

1. Greater susceptibility of females than of males to alloxan diabetes, a sex difference not eliminated by prepubertal gonadectomy.

2. Marked and delayed hypoglycemic phase of the alloxan reaction occurring at about the 24th to 37th hours after injection.

3. Inability of severely diabetic animals to maintain high fasting blood sugars and the frequent occurrence of severe fasting hypoglycemia, a demonstration that alloxan diabetes in Wistar rats is of a complex and unorthodox type.

It seemed strange that these characteristics of alloxan diabetes, so marked in the Wistar derivative, were not described by other workers who have observed alloxan treated rats. It appeared likely that the explanation might lie in strain differences. The present work, which explores this possibility, demonstrates that such a strain difference does in fact exist and implies diversity between strains in endocrine endowment relating to carbohydrate metabolism.

EXPERIMENTAL

Observations of the alloxan reaction in 72 male and 72 female albino rats of Wistar origin which were reported previously[1] are compared herein with those from a similar experiment using 68 male and 66 female albinos of the Osborne-Mendel strain.* These were bred in our own colony from descendants of a small stock secured from The Connecticut Agricultural Experiment Station in New Haven.† In designing the work the Osborne-Mendel rat seemed of special significance because investigation of this hereditary line in other laboratories has demonstrated it to be physiologically unique. Not the least interesting characteristic of the strain from our viewpoint is its normally lowered tolerance for glucose which was discovered by Cole and Harned[4] and referred to by them as the "diabetic trait."

Animals in the age range of 200 to 280 days were used. These were fasted 96 hours prior to injection of alloxan monohydrate (Eastman) which was given in 3 per cent solution subcutaneously in a dose of 20 mg. of the monohydrate per 100 gm. body weight. Fifteen minutes after injection the animals were given their usual ration of Purina Laboratory Chow *ad libitum*. Blood samples for glucose determination were taken from the tail before alloxan was given and at various intervals thereafter up to 61 hours. Not more than eight or nine samples of 0.1 ml. volume were

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*The Osborne-Mendel strain of albino rat is a pure line maintained by The Connecticut Agricultural Experiment Station having been bred there since 1910 without accessions from elsewhere. It originated from a few animals purchased in a local pet shop by Thomas B. Osborne for some early nutrition work at the Experiment Station. This breed of rat was used in the now classic experiments in nutrition by Thomas B. Osborne in collaboration with Lafayette B. Mendel of Yale University. Thus, although the parent breeding colony has always remained at The Connecticut Agricultural Experiment Station, it sometimes has been referred to as the "Yale strain." The development of this stock as regards its accelerating growth rate over the years of inbreeding and special nurture is described by Osborne and Mendel[5] and later by Mendel and Hubbell.[6]

†The authors are grateful to Dr. Hubert B. Vickery and Dr. Rebecca B. Hubbell for breeding stock from The Connecticut Agricultural Experiment Station colony.

taken from any one animal to avoid excessive handling and blood loss.

A variety of measures was used to assess the resulting diabetic state. Postprandial blood sugar was determined one and three weeks after alloxan and the fasting glucose tolerance two weeks after alloxan. At one and three weeks also, urinary glucose and acetone (qualitative) were determined on samples collected during a standard 18-hour period on a diet of fluid milk. During this period a record of body weight was maintained. The details of these tests and methods are described in an earlier paper.[1]

RESULTS

The over-all incidence of diabetes in alloxan treated rats among the two strains is presented in table 1. Here it is seen that the Osborne-Mendel animals evidence a far greater sensitivity to the compound than those of Wistar origin. Of 144 Wistar rats so treated, only 31 terminated fatally whereas there were 62 fatalities among 134 Osborne-Mendel rats. Twenty-six per cent of the Wistar males but only nine per cent of the Osborne-Mendel males were resistant to alloxan. It is clear that while the two strains differ from each other in sensitivity to alloxan both strains show the same sort of sex divergence in susceptibility, namely, that the females are more severely affected than the males, a difference originally demonstrated in the Wistar strain.[1] Sixty-three per cent of the Osborne-Mendel females but only 30 per cent of the corresponding males developed diabetes which terminated fatally. Although alloxan treated animals classed in the subgroup "Fatal" under "Severe Diabetes" died with high blood sugars and had every evidence of severe diabetes, it is possible that other toxic damage may have contributed to the fatal issue, for it is well known that alloxan injury is not limited exclusively to the pancreas.

Comparison of established severe alloxan diabetes in the two strains of animals in the postprandial state is furnished by table 2. As regards blood sugar level, males and females of both strains are about comparable showing averages in the range of 400 to 450 mg. per 100 cc. Likewise, urinary glucose levels are not very different though all groups show a wide variability as indicated by large standard deviations. Strain and sex differences are apparent however in the matter of urinary ketone body excretion. That the Osborne-Mendel strain is more susceptible to ketonuria is demonstrated by the fact that three weeks after alloxan injection 4 per cent of the Wistar male diabetics and 72 per cent of the Osborne-Mendel male diabetics show ketonuria. The sex difference originally observed in diabetic ketonuria in the Wistar strain[1] is not as readily apparent in the Osborne-Mendel strain on the basis of the present data. A lower proportion of Osborne-Mendel males than females show ketonuria one week after alloxan but by three weeks the qualitative incidence appears the same. However, if quantitative estimates of urinary ketone bodies had been made the sex difference might also have been apparent in Osborne-Mendel rats at the third week, for many of the males at that time evidenced faint traces of acetone while the females gener-

TABLE 1
Diabetes in alloxanized rats

Animal Strain	Type Reaction*	Male No.	Male Per cent	Female No.	Female Per cent
WISTAR	Severe diabetes	40	56	64	89
	Fatal	12	17	19	26
	Mild or transient diabetes	13	18	2	3
	Resistant	19	26	6	8
	Total	72		72	
OSBORNE-MENDEL	Severe diabetes	57	84	62	93
	Fatal	20	30	42	63
	Mild or transient diabetes	5	7	1	2
	Resistant	6	9	3	5
	Total	68		66	

*Type reaction.

Severe diabetes—Marked glycosuria in both strains ranging from 4.0 to 12.0 per cent. If not terminated fatally the postprandial blood sugar at three weeks was above 270 mg. per 100 cc.

Weight loss was generally observed in these animals during the three week period and was more severe in the Osborne-Mendel animals amounting to 10 to 35 per cent of the body weight.

Fatal (subgroup)—Developed severe diabetes but failed to survive one week after injection of alloxan.

Mild or transient diabetes—Showed some symptoms of diabetes but by three weeks had recovered or showed postprandial blood sugars below 270 mg. per 100 cc. Little or no glycosuria at three weeks and no weight loss.

Resistant—All others.

TABLE 2
Blood sugar, glycosuria and ketonuria in alloxan diabetic rats

Animal Strain	Number and Sex	Time After Alloxan	Postprand. Bloodsugar	Average Urine Vol.	Urine Glucose*	Cases Showing Ketonuria†
		Weeks	mg./100 cc.‡	ml.	gm./100 cc.	Per cent of total
WISTAR	28 Males	1	402±79	41	4.7±2.0	12
		3	424±74	55	5.7±1.1	4
	45 Females	1	426±74	50	6.3±1.8	50
		3	418±72	54	7.0±1.7	61
OSBORNE-MENDEL	37 Males	1	439±68	33	7.2±2.7	38
		3	442±89	49	7.5±2.7	72
	20 Females	1	436±57	28	7.2±2.6	70
		3	457±52	42	7.2±1.8	75

*During this test animals are placed in metabolism cages for an 18 hour period, given water *ad libitum* and whole fluid milk up to a total volume of 60 ml.
†The ketone body test was applied to the same urine sample on which glucose was determined.
‡± indicates standard deviation.

ally showed more substantial amounts.

The dramatic succession of blood sugar changes which occurs during the first 48 hours following alloxan injection, referred to usually as the "triphasic response," has interested nearly all workers who have dealt with this type of diabetes. Figures 1 and 2 present such a study on males and females respectively of the Wistar strain and may be compared with figures 3 and 4 relating to the Osborne-Mendel strain. The data on the sexes have been separated to reveal the sex difference as well as the marked contrast between the two strains. In Wistar stock hyperglycemia increases progressively during the first 20 hours after injection and this is followed by the rapidly-developing, transient relative hypoglycemia. This characteristic low blood sugar phase is observed in every Wistar animal. In a large percentage of the reacting Wistar rats, particularly the more susceptible females, the hypoglycemia is "real" with blood sugars falling well below normal fasting levels. By way of contrast, males of the Osborne-Mendel stock are completely resistant to the development of the hypoglycemic phase, while the Osborne-Mendel females show but a slight tendency to falling blood sugar in the 24 to 30 hour interval.

Most important in the assessment of alloxan diabetes is the oral glucose tolerance test after a 24 hour fast. Data on this test applied to alloxan diabetic and normal subjects of both animal strains are presented in table 3. To emphasize fully the outstanding features of variability in alloxan diabetes within as well as between strains, the high, low and median values and the first and third quartile limits in addition to average values are presented. Animals of the Wistar line in severe diabetes are characterized by relatively low fasting blood sugars. A significant fact is that some of them develop a real hypoglycemia and may even become convulsive, behavior not explainable on the basis of relative supply of insulin alone. In contrast, the Osborne-Mendel line shows generally an intense fasting hyperglycemia with only one male in the present group developing a normal fasting blood sugar and no instance of fasting hypoglycemia. Attention is also called to the fact that the average glucose tolerance curve in the Osborne-Mendel diabetics falls less steeply from the 0.5 to the two-hour period and is thus more typically diabetic than that of the Wistar animals. These differences are especially noteworthy when it is recalled that the diabetic animals of both strains appear to have equal glycosuria and hyperglycemia when fed.

Cole and Harned[4] and later Orten and Devlin[7] demonstrated that untreated Osborne-Mendel rats have an impairment in glucose tolerance compared with Wistar rats. While this difference is hardly apparent in the normal data in table 3, the present results can be explained in that they were obtained by the use of a much less taxing glucose tolerance load.

DISCUSSION

After Cole and Harned's[4] finding that the Osborne-Mendel strain rat may develop progressive impairment of glucose tolerance with age,* Cole, Harned and Keeler[8] studied the genetic aspects of this "diabetic trait" and concluded that the sire exerts a greater influence than the dam upon the glucose tolerance of

TABLE 3
Oral glucose tolerance test* after 24 hour fast

	Wistar					
	Male (26)†			Female (35)		
Time after glucose hour	0	0.5	2	0	0.5	2
Normal Average	86±6‡	125±7	90±6	89±7	128±8	91±6
Alloxan diabetic						
Average	115±49	252±49	141±53	150±73	276±78	178±80
Highest value	239	378	265	309	435	329
1st quartile	138	290	180	215	356	252
Median	94	253	132	123	262	170
3d quartile	83	224	109	94	235	119
Lowest value	62	165	62	47	129	44
	Osborne-Mendel					
	Male (37)			Female (20)		
Time after glucose hour	0	0.5	2	0	0.5	2
Normal Average	97±14	132±23	105±31	83±7	136±10	97±7
Alloxan diabetic						
Average	251±91	382±106	329±97	289±89	431±70	366±86
Highest value	454	672	484	568	548	572
1st quartile	326	444	384	327	476	409
Median	272	388	332	285	436	362
3d quartile	165	328	284	237	394	327
Lowest value	94	138	111	138	264	188

*Tests were made on alloxan treated animals two weeks after alloxan injection; 100 mg. glucose per 100 gm. body weight in 20 per cent solution were given by mouth.
†Figures in parenthesis show number of cases represented in average values.
‡± indicates standard deviation.

the offspring. Harned and Cole have proposed that this difference between the Osborne-Mendel and the Wistar strains is due to a difference in anterior pituitary function. As evidence of hyperactivity of the anterior pituitary in the Osborne-Mendel strain they point out its greater hyperglycemic response to epinephrine, a mild degree of insulin resistance, increased urine volumes, accelerated growth rate and higher incidence of sterility. During the long history of the breeding of the Osborne-Mendel strain a remarkable acceleration of growth rate has occurred,[5, 6] and while this enhanced capacity to grow has been largely attributed to improved dietary regimen[10] it also presupposes pituitary growth hormone production at a rate permissive of such growth. The Osborne-Mendel strain reaches a body size one quarter to one third greater than that of the Wistar strain but frank gigantism is not observed. Orten and Sayers[11] have demonstrated that the Osborne-Mendel rat has a diminished ability to store liver glycogen compared with the Wistar rat and they believe it is this condition rather than lack of insulin which causes the "diabetic trait."

All of the comparative work on the two strains of rats, including our present observations, indicate a marked divergence between them and differences in endocrine endowment almost certainly are responsible in part at least. It is, of course, not certain that all of the unique characteristics of the Osborne-Mendel strain compared with the Wistar can be explained on the basis of a single heredifary difference.

If the hypoglycemic phase in the response to alloxan action is due to an outpouring of insulin from the damaged beta cells of the pancreas, as is commonly thought, the absence of any marked hypoglycemia in the Osborne-Mendel rat under these circumstances sug-

*After two years of observing the Osborne-Mendel strain in our own breeding colony, we have found among about 200 males one that at maturity spontaneously developed frank diabetes with continuous glycosuria and hyperglycemia. In all other respects the animal was normal and seemed vigorous.

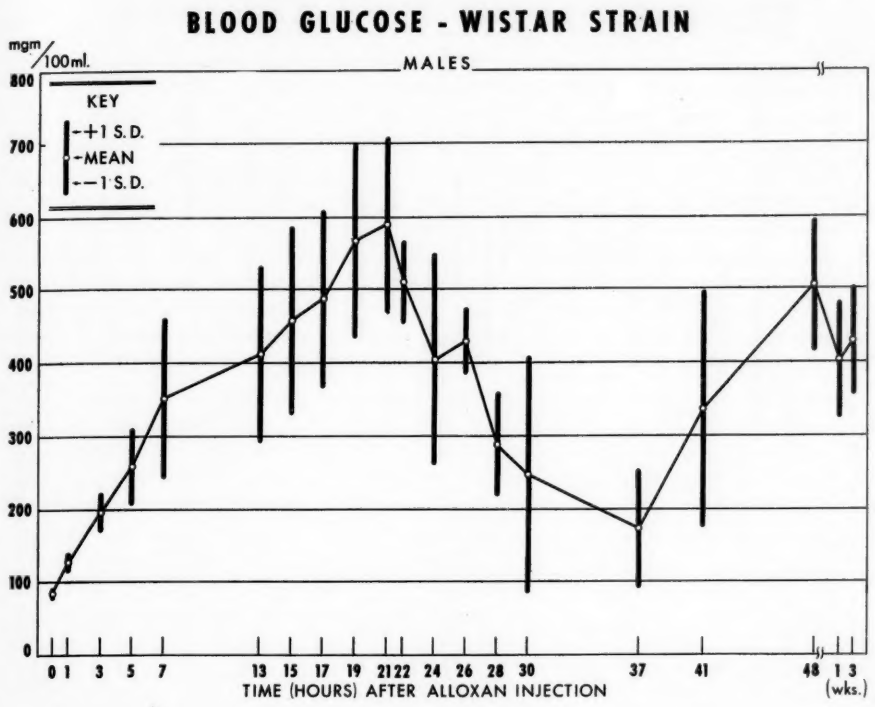
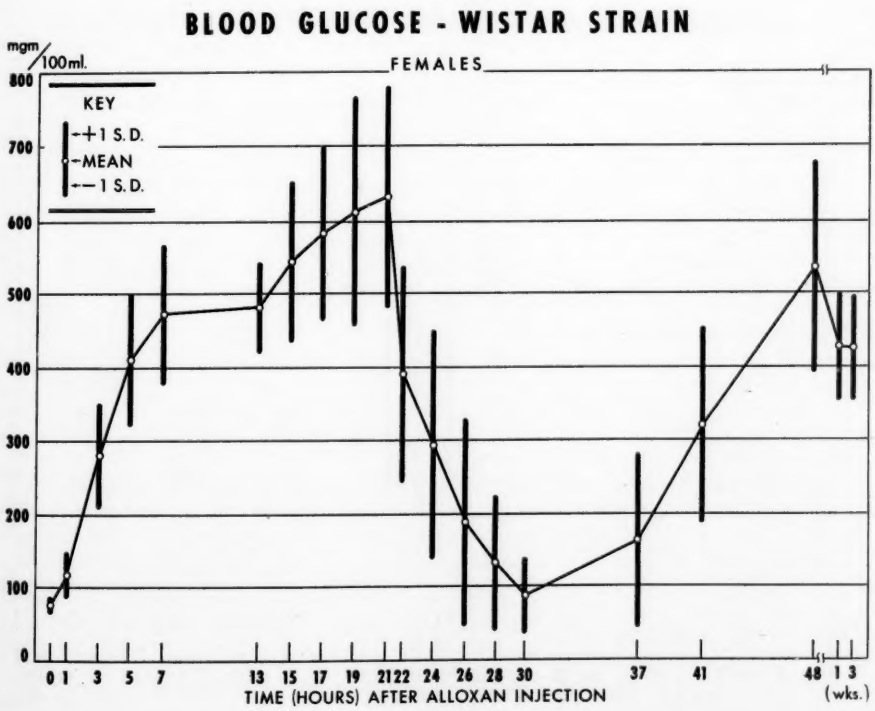


FIGURE 1



Blood sugar changes after alloxan. Data on only those animals developing severe diabetes and surviving at least one week after alloxan injection. Prior to alloxan injection animals were fasted four days. Fifteen minutes after alloxan, food was given ad libitum for the duration of the experiment.

FIGURE 2

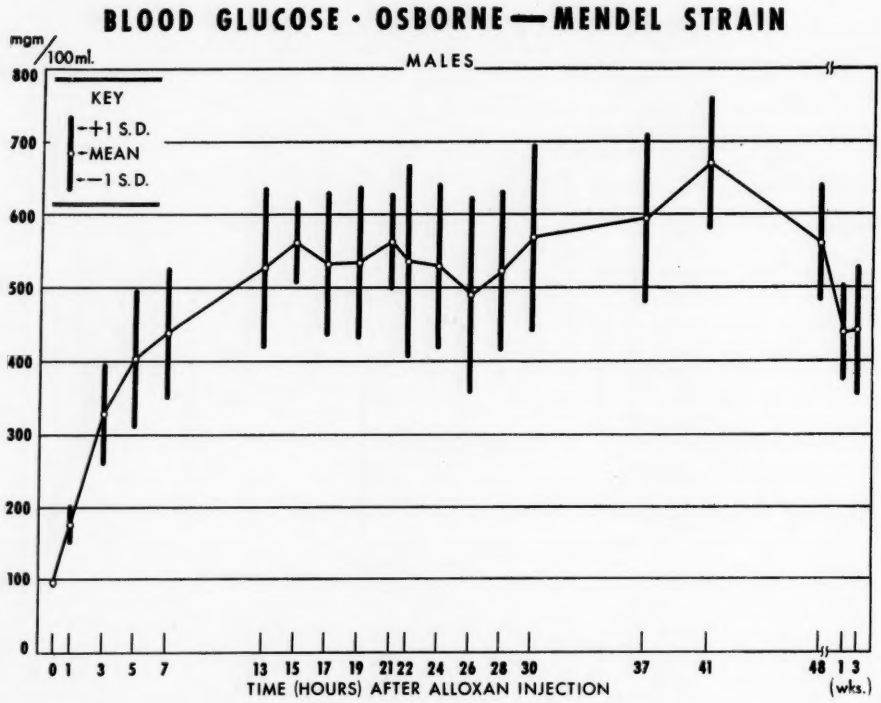


FIGURE 3

Blood sugar changes after alloxan. Data on only those animals developing severe diabetes and surviving at least one week after alloxan injection. Prior to alloxan injection animals were fasted four days. Fifteen minutes after alloxan, food was given ad libitum for the duration of the experiment.

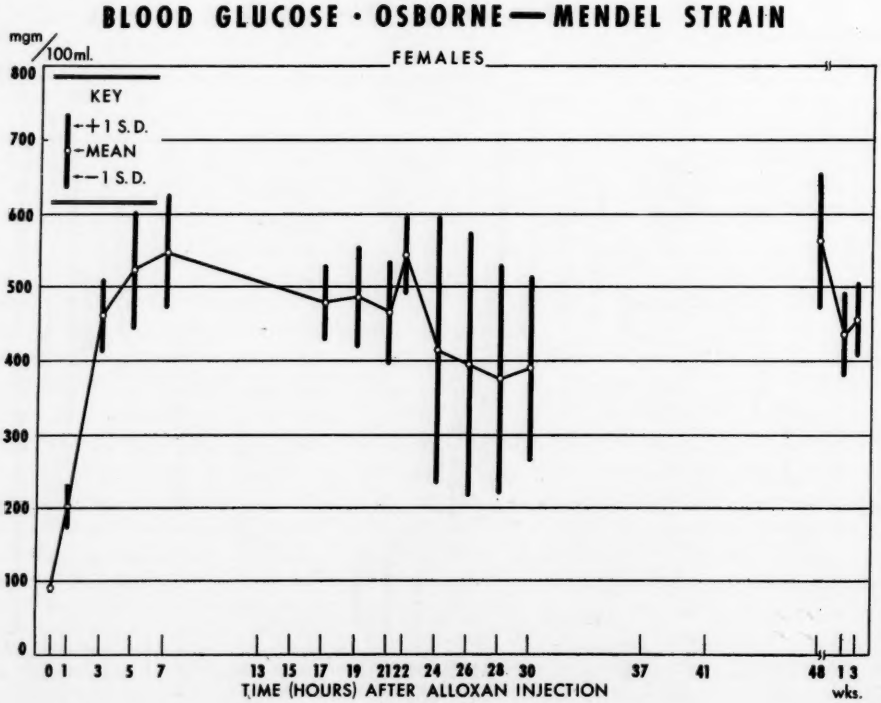


FIGURE 4

gests either a virtual absence of insulin reserves in the pancreas or an insulin resistance not shared by the Wistar strain. In connection with this absence of a pronounced triphasic response in the Osborne-Mendel strain, it is perhaps of special significance to consider the possible role of liver glycogen storage as the mechanism for producing the hypoglycemic phase. Cullimore and others[3] demonstrated that in the Wistar animals the hypoglycemic period was simultaneous with a period of elevated liver glycogen. The observation of Orten and Sayers[11] that the Osborne-Mendel rat has an impairment in the mechanism of liver glycogen storage suggests this as a possible cause of the failure of the strain to give a typical response to alloxan.

The additional difference between the two strains of rats in respect to fasting blood sugar and form of glucose tolerance curves after induction of alloxan diabetes presents difficulties of interpretation. The assumption that insular tissue in the Osborne-Mendel rat is more susceptible to alloxan and consequently that more severe diabetes is produced is attractive and would be sufficient to explain all except the group of Wistar diabetics which develop real hypoglycemia in fasting. It is in this group of animals, which resemble hypophysectomized or adrenalectomized animals, that the diabetes is believed to be modified by some factor other than insulin supply. Experiments are now in progress to examine further points of difference in carbohydrate economy of these two contrasting albino rat strains that might shed some further light on the present problem. Previous work from this laboratory[2] has demonstrated that the gonads have a considerable effect upon the diabetic state produced by alloxan. Castrates of both sexes, in which alloxan diabetes was subsequently induced, show more elevated fasting blood sugars and prolonged tolerance curves than intact control diabetics. This emphasizes one way in which alloxan diabetes depends upon the balance of extrapancreatic endocrine factors, a point of view not inconsistent with current research and clinical opinion regarding spontaneous diabetes.

SUMMARY

A comparative study of alloxan diabetes in the Osborne-Mendel and the Wistar strains of albino rat is reported. The Osborne-Mendel strain differs from the Wistar strain in: (1) greater susceptibility to alloxan; (2) failure to develop any severe hypoglycemic response to alloxan during the 48 hours following its administration; (3) greater susceptibility of the alloxan diabetic males to ketonuria; (4) more elevated fasting blood sugars in severe alloxan diabetes; and (5) more elevated and prolonged diabetic glucose tolerance curves. The findings are discussed with reference to other work that has demonstrated abnormalities in the Osborne-Mendel strain.

SUMMARIO IN INTERLINGUA

Diabete Alloxanogene in Rattos Albin, Influentiate per Differentias de Racia

Es reportate un studio comparative de diabete alloxanogene in le racias Osborne-Mendel e Wistar de rattos albin. Le racia Osborne-Mendel differe ab le racia Wistar in (1) su plus grande susceptibilitate a alloxano, (2) absentia de sever responsas hypoglycemic a alloxano durante 48 horas post su administration, (3) un plus grande susceptibilitate del masculos a cetonuria, (4) plus elevate nivellos de sucro sanguinee in stato jejun in sever casos de diabete alloxanogene, e (5) plus elevate e prolongate curvas de tolerantia a glucosa. Nostre constatationes es discutite con referentia a altere studios que ha demonstrate anormalitates in le racia Osborne-Mendel.

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Serum Lipids in Diabetic and Nondiabetic Rats

Effect of Varying Lipid Diets

R. N. Cagan, M.D., R. Nichols, B.A., and Leo Loewe, M.D.,† Brooklyn*

Since the pre-insulin era, treatment of diabetes by a high fat diet has been an accepted therapy. Little question exists as to the efficacy of this diet in aiding diabetic control. However, as diabetics live longer in our present insulin age, more are succumbing to arteriosclerotic vascular disease. Since considerable evidence exists relating high blood lipids to the development of arteriosclerosis, the efficiency with which a diabetic animal metabolizes excess fat becomes a pertinent question.

Early work with diabetic dogs revealed an abnormally high lipemia in those fed high fat diets.[1] And recent work in humans showed a decreased tolerance for ingested cholesterol by diabetics.[2]

The following investigation was performed in order to determine the tolerance of the uncontrolled diabetic rat to ingested cholesterol, phospholipid and fatty acid.

METHODS

Male rats of the Wistar strain weighing 200 to 250 gm. were divided into control and diabetic groups. Half the number of animals in each group were placed on a diet containing 47 per cent cocoanut oil, 16 per cent cholesterol, 10 per cent phospholipid (from dried egg yolks), 26 per cent powdered Rockland Mouse Diet and added supplements of Vitamins B and C and Calcium Gluconate. The control normal and diabetic animals were fed the Rockland Mouse Diet with similar supplements.

We recognize that previous investigators have fed more physiologic quantities of cholesterol in their high fat diet. However, because of our interest in producing vascular lesions and because of the difficulties in previous attempts to do so in rats, we decided to use the noted high dosages of cholesterol. On this diet the animals gained as much as or more weight than did the control or diabetic animals on the normal diet. The rats were weighed weekly. Table 1 is a summary of the variations in weights in each group.

TABLE 1
Changes in rats' weights per week (grams)

	Control diet	Lipid diet
Normal	+ 5 to +15	+10 to +20
Diabetic	−20 to + 5	− 5 to +15

It was our chief objective to determine whether the diabetic animals on a high lipid intake suffered any abnormality in their tolerance of lipids. Although analysis of fasting sera may have resulted in more uniform results, lipemia is most prominent postprandially. Thus, if any abnormal lipid tolerance were to be detected, it would be more obvious after eating. In view of these facts, the experiment was conducted on nonfasting rats permitted to eat their respective diets as desired. The animals' food cups were kept full at all times and blood was drawn always at the same time of day, between 9:30 and 10:30 a.m.

Diabetes was induced by three subcutaneous injections of 60 mg. of alloxan on successive days when a nonfasting blood sugar usually revealed a blood glucose of 200 mg. per 100 ml. or more. If necessary, a fourth injection was given.

Diabetic animals were maintained for twelve to sixteen weeks before their serum lipids were examined. Nonfasting blood sugars were obtained every two weeks. Those showing blood sugars below 190 mg. per 100 ml. were treated with alloxan again until their blood glucose reached 200 mg. per 100 ml. About two-fifths of the diabetic animals required additional alloxan treatment.

Blood for lipid determination was not taken from a diabetic animal appearing terminally ill or from one that had its alloxan less than seven days previously. It was desirable that animals with only mild or moderate diabetes be used lest terminal shock or dehydration become factors causing important alteration of the animals' serum lipid.

Blood was taken from animals maintained on a high lipid diet for ten to twelve weeks. About three milliliters were obtained for analysis by cardiac puncture of the nembutal-anesthetized rat. Serum total cholesterol,[3] total fatty acids,[4] lipid phosphorus[5, 8] and a final blood sugar[6]

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were determined.

All analyses were made in duplicate. Recoveries and standards of cholesterol, palmitic acid and inorganic phosphorus were used to control the determinations of the respective blood lipid components. A determination was considered valid, if the following criteria were fulfilled for each series:

1. Duplicates within 2 per cent.
2. Duplicates on known cholesterol solution between 98 and 102 mg. for 100 mg. per 100 ml.
3. Duplicates on known inorganic phosphorus solution between 9.8 and 10.2 mg. for 10 mg. per 100 ml.
4. Duplicates on a known palmitic acid solution between 39.0 and 41.0 mEq. for 40.0 mEq/L.
5. Recoveries from sera of cholesterol (97 to 102 mg.), inorganic phosphorus (9.8 to 10.2) and palmitic acid (39.0 to 41.0 mEq.) were required after the above noted quantities of the respective lipids had been added.

RESULTS

One may observe from table 2 that the normal animals on a high lipid diet (group 3) have significantly elevated serum lipids. The values for the serum lipids in this group are significantly* elevated over those serum values found in the rats of group 1 (nondiabetic on normal diets). In the latter group serum total cholesterol was 47.1 mg. per 100 ml., total fatty acids 10.7 mEq/L., and lipid phosphorus 4.3 mg. per 100 ml. These values compare with the respective values in group 3 of 85.4 mg., 18.7 mEq., and 5.4 mg.

The diabetic animals on a control diet (group 2) may be seen from the table to have significant elevations only in the serum fatty acid component. This value, 22.3 mEq/L., may be compared with 10.7 mEq. in the serum of the control rats in group 1.

Upon comparing the serum lipids in normal rats, groups 1 and 3, and diabetic rats, groups 2 and 4, the increment in each serum lipid component from groups 1 to 3 and from groups 2 to 4 reveals that normal rats on a high lipid diet (group 3) have an average increase in serum lipids over the respective values in the normal rats on a control diet (group 1) of 38.3 mg. of cholesterol per 100 ml. of serum, 8.0 mEq. of fatty acid per liter of serum, and 1.1 mg. of lipid phosphorus per 100 ml. of rat serum. These values compare with the respective increases in the serum lipid components from group 2 (the diabetic on control diet) to group 4 (the diabetic on a high lipid diet) of 75.1 mg. of cholesterol, 6.4 mEq. of fatty acid, and 2.9 mg. of lipid phosphorus. *The serum elevations of cholesterol and of lipid phosphorus were significantly higher in the diabetic group.* However, the increase in serum fatty acids was approximately the same in both groups.

An additional observation was that the sera of the diabetic animals on a high lipid diet (group 4) always were lipemic. The normal animals on a control diet never revealed lipemic sera while group 2 and 3 animals had lipemic sera only 20 per cent of the time. Furthermore, the degree of lipemia was far more intense in group 4.

DISCUSSION

It is a well established fact that ingestion of fat results in a rise in serum lipids. Our data are in agreement, for both the normal and diabetic rats when fed a high fat diet (groups 3 and 4) revealed marked elevation of their serum lipids above the respective values in the groups fed control diets (groups 1 and 2).

The present data from the diabetic rats (group 2) reveal that only the total serum fatty acids were elevated significantly above those values in normal rats. The serum cholesterol and phospholipid showed no change. These facts differ from our previous findings in diabetic rats on a normal diet.[8] However, the previously reported study dealt with rats acutely diabetic, that is, for two

* All calculations for statistical significance are based on formulae from R. A. Fisher's text.[7]

TABLE 2

The serum lipids and blood glucose of intact and alloxan-diabetic rats maintained on control and high-fat diets

				Serum lipids, average values with S.D.				
Group number	Diet	Animal condition	Number in series	Total cholesterol mg./100 ml.	Total fatty acids mEq/L.	Lipid phosphorus mg./100 ml.	Lipemia % of animals	Blood glucose (final) mg./100 ml.
1	Control	Normal	13	47.1(±12.5)	10.7(±3.1)	4.3(±0.43)	0	99±17
2	Control	Diabetic	13	50.4(± 7.3)	22.3(±9.0)*	4.8(±0.25)	23	287±90
3	Lipid	Normal	12	85.4(±12.0)*	18.7(±5.5)*	5.4(±1.12)*	17	120±27
4	Lipid	Diabetic	15	125.5(±31.0)†	28.7(±8.0)	7.7(±1.51)†	100	329±79

*Elevation from group 1 is mathematically significant (p=less than 0.01).
†Elevation from group 2 is mathematically significant (p=less than 0.01).

to ten weeks. The fact that the rats in the present study had suffered diabetes for a prolonged period suggests that their metabolism had greater opportunity to adjust, that the severity of the diabetes ameliorated, or that the fat deposits had become depleted. The explanation for persistence of the elevation in the fatty acid component in the diabetic group on control diet (group 2) may be found in Gurin's work.[9] He showed that lack of insulin prevents incorporation of the short chain fatty acids into the normal metabolic channels and therefore results in accumulation of the shorter chain acids as fat deposits became depleted.

Upon comparing the *elevation* in serum lipids in nondiabetic animals fed a high fat diet with the rise in serum lipids in diabetic animals fed a similar diet, significant differences are uncovered in the cholesterol and phospholipid components of the two groups. The increase in fatty acids is about the same. The rise in the total cholesterol of the diabetic rats (group 4) is almost double that of the nondiabetic group on a similar diet (group 3). Whether this defect in capacity to utilize cholesterol by the diabetic rat may have significance in the development of arteriosclerosis in these animals cannot be answered at this time. The experimental production of arteriosclerotic lesions in the rat is a notoriously difficult procedure. But, certainly in view of the accelerated development of arteriosclerosis in the diabetic human, and in view of the relationship of cholesterol feeding and resultant arteriosclerosis in the rabbit, it is interesting to speculate that perhaps a decreased tolerance for cholesterol in the diabetic accentuates the arteriosclerosis. This possibility becomes more real if one realizes that recent studies suggest that the bulk of cholesterol deposition in experimental arteriosclerosis is from exogenous sources.[10, 11]

Why do the diabetic animals suffer a decreased tolerance for ingested cholesterol? Is the (alloxan-diabetic) rat's liver defective or is its cholesterol excretory mechanism somehow impaired so that exogenous cholesterol cannot be metabolized at the usual rate? The probability is that the surplus exogenous fat in the form of fatty acids and phospholipids fed to these animals is broken down and resynthesized to cholesterol. For, in accordance with Brady and Gurin's work, the diabetic liver can no longer convert acetate to the long chain fatty acid, but can synthesize cholesterol at the usual rate. Thus, the diabetic animals on a high fat diet (group 4) suffered a rise in serum cholesterol not only because they were fed cholesterol but also because they were fed other fats. These fats could be broken down and resynthesized to cholesterol but no longer into fatty acids. Therefore, since the usual channels for resynthesis of longer chain fatty acids from the two carbon fragments were blocked because of insulin lack, the formation of cholesterol was facilitated.

The additional finding of a *greater* increment in the serum phospholipid in the diabetic animals (groups 2 to 4) when compared to the increase in the control rats (groups 1 to 3) can be explained similarly. The liver, small intestines and kidneys of animals with no insulin have a higher than normal phospholipid synthesis.[12] In view of this fact, we can understand that the diabetic rats fed abnormal quantities of cephalin and fatty acids have an increase in their serum phospholipid not only because of the administered cephalin but also (in contrast to the nondiabetic) because they are reforming larger quantities of degraded fatty acid fragments to phospholipid.

The observation that the diabetic rats on a high lipid intake (group 4) was the only group to provide sera which was consistently lipemic is only a corroboration of the fact that this group yielded sera with the highest absolute values for total fatty acids. This finding is in agreement with turbidometric studies done on normal and diabetic postprandial, human sera.[13]

SUMMARY

1. Sera of control and alloxan-diabetic rats on normal and high lipid diets were analyzed for total cholesterol, lipid phosphorus and total fatty acids.

2. Sera of nonfasting control rats on a high lipid intake revealed significant elevations above the control group on normal diet in all three lipid components. The sera of diabetic rats on a high lipid diet showed mathematically significant elevations over their controls only in the cholesterol and phospholipid components.

3. Rats, diabetic for more than twelve weeks, and on a normal diet, revealed significant elevations only in the serum fatty acids. Serum cholesterol and lipid phosphorus were not elevated.

4. Comparison of the *increases* in serum lipids between the diabetic (group 2 and 4) and the nondiabetic (group 1 and 3) groups revealed that the diabetic animals on a high lipid intake sustained significantly higher *elevations* in the cholesterol and phospholipid components.

5. The metabolic mechanisms which are thought to facilitate abnormal increases in serum cholesterol and phospholipid while maintaining a "brake" on the increase in the serum fatty acid in the diabetic animals on a high lipid diet are discussed.

SUMMARIO IN INTERLINGUA

Lipidos Seral in Diabetic e Nondiabetic Rattos a Dietas Normal e Ric in Lipidos

1. Seros ab rattos de controlo e ab rattos con diabete

alloxanogene, mantenite con dietas normal e con dietas ric in lipidos, esseva analysate pro cholesterol total, phosphoro lipidic, e acidos grasse total.

2. Seros ab nonjejun rattos de controlo con un ingestion ric in lipidos revelava significative elevationes supra le gruppo de controlo con dietas normal, relative a omne tres componentes lipidic. Le seros de rattos diabetic con un dieta ric in lipidos monstrava mathematicamente significative elevationes supra le controlos solmente in relation a lor componentes cholesterolic e phospholipidic.

3. Rattos que esseva diabetic pro plus que 12 septimanas e que recipeva dietas normal revelava significative elevationes solmente in le acidos grasse del sero. Cholesterol e phosphoro lipidic in le sero non esseva elevate.

4. Le comparation del augmentos in lipidos seral in (1) le gruppos diabetic e (2) le gruppos nondiabetic revelava que le animales con un plus alte ingestion lipidic experientiava significativemente plus alte elevationes del componentes cholesterolic e phospholipidic.

5. Le mechanismos metabolic que es possibilemente involvite in facilitar anormal augmentos del cholesterol e del phospholipidos del sero durante que illos mantene un influentia restringente super le augmento del acidos grasse del sero in animales diabetic que recipe un dieta ric in lipidos es discutite.

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Social Attitude Toward Invention

Today we have thousands of scientists for every one (in the modern sense) that existed a century ago. But the vast majority of today's scientists—often the most competent—are engaged not in invention of fundamentally new principles, processes, or things, but in development and in various essential forms of technical service. Our society often lures even the scientist of highest integrity away from his dreams to become a well-paid cog in organized research. Business is aware of this difficulty and tries to compensate by generous contributions to academic training, but it is questionable whether this accomplishes anything more than enlargement of the pool of talent from which to recruit its technical staff.

The present social attitude toward invention in the United States is one of complete acceptance of any sort of development announced by a responsible agency. In general, public skepticism is a thing of the past. But this represents less change than it seems, for a century ago there were few responsible agencies in the modern sense. New things were promoted largely by impecunious individuals who would inspire about as little public confidence today as they did then. Respect is given today not to individual technologists (as a rule) but to the institutions they represent. In one sense we seem to be drifting backward toward the attitude of the seventeenth century for at no time in history has conformity been more important than it is today. And this applies to both sides of the iron curtain. In Russia it is dangerous not to conform. Here it is economically inadvisable, and most of us want to make a living.

Eugene Ayres in *American Scientist* 40: 521-40, October 1955.

Serum Lipids and Polysaccharides in Diabetes Mellitus

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New York

Independent observations indicate that elevations of serum lipids[1-5] as well as serum polysaccharides[6-9] occur in diabetic patients with specific degenerative vascular complications. No comparative study of these groups of substances in the serum has been performed in the same diabetic patients with special reference to the presence or absence of degenerative vascular disease.

This study presents a simultaneous correlative analysis of the serum lipid partition, serum total cholesterol, esterified cholesterol, phospholipids, neutral fats and total lipids, and the serum glucosamine and total polysaccharides bound to serum protein in a group of 66 patients with diabetes mellitus.

SELECTION OF PATIENTS

The patients included in the study did not present any stigmata associated with idiopathic hypercholesteremia or idiopathic hyperlipemia; nor did they exhibit evidences of diseases such as myxedema or biliary cirrhosis, known to affect the concentration of serum lipids, or such diseases as cancer, acute or chronic infections and acute myocardial infarction, known to influence the concentration of serum polysaccharides.[10-15]

Group I consisted of persons who were found to be in good health and were examined as controls during the time of the study. Their ages were comparable with those of the following groups. The control values on serum lipids were obtained from 73 patients between the ages of 48 to 52 years.[16] Similarly the control studies on serum glucosamine and polysaccharides were performed on 15 nondiabetic persons.[8] In contrast to Groups II, III and IV, simultaneous studies were not performed in the controls of Group I.

Group II consisted of 38 patients with uncomplicated diabetes. The average duration of diabetes was 8.4 years, range 1 to 16 years. The average age of the group was 50.2 years. Eighteen of these patients required no insulin, 15 used between 10 to 30 units, 3 used 35 to 50 units and 2 over 55 units daily. Patients with proteinuria, renal insufficiency, retinopathy, neuropathy, coronary artery, and peripheral vascular disease established by clinical, laboratory, and roentgen examination were carefully excluded. The average fasting blood sugar of the group was 128 mg. per 100 cc. The systolic blood pressure exceeded 150 in 7 instances (152 to 170 mm.) and averaged for the group 139 mm. The diastolic blood pressure exceeded 90 mm. in 5 instances only (92 to 104) and the average for the group was 84 mm.

Group III included 12 specially selected patients with early diabetic retinopathy and no evidences of hypertensive retinopathy, proteinuria or renal inadequacy. The duration of diabetes was 2 to 25 years, average 13 years. The average age of the group was 54.3 years. Only one patient of this group required no insulin, 7 used 10 to 30 units, 2 used 35 to 50 units, and 2 used 55 to 60 units daily. The average fasting blood sugar of the group was 137 mg. per 100 cc. The average systolic blood pressure was 155, the average diastolic blood pressure 89 mm.

Group IV consisted of 16 patients with the fully developed Kimmelstiel-Wilson syndrome. Severe retinopathy, hypertension, edema, proteinuria, and doubly refractile lipids in the urine were the outstanding features. In many cases there was evidence of renal insufficiency; six were in congestive heart failure, partially compensated by medication. The known duration of diabetes was 1 to

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29 years, average 13.4 years. The average age of the group was lower than that of the preceding two groups: 45.1 years. Three patients required no insulin while 8 used 10 to 30 units, three 40 to 60 units and two 65 to 90 units daily. The average fasting blood sugar was 134 mg. per 100 cc. The average blood pressure was elevated to 194 mm. systolic and 115 mm. diastolic.

METHODS

Twenty to forty milliliters of blood were drawn from subjects after a fast of 12 to 14 hours. The sera was separated within the next 2 to 6 hours and stored in a refrigerator until they were analyzed within the next 4 to 24 hours. Hemolyzed specimens were not used.

Serum cholesterol and esters were analyzed by the method of Sperry and Schoenheimer,[17] phospholipids by Sperry modification of Fiske-SubBarow method,[18] total lipids by the gravimetric method of Bloor.[19] Neutral fats were estimated by subtracting the sum of total cholesterol and phospholipids from total lipids.

Serum glucosamine was determined by the procedure of West and Clarke.[11] Total polysaccharides bound to serum protein were determined by the method of Graff and co-workers.[20]

RESULTS

The data obtained are summarized in table 1. It is evident that Groups I and II exhibit no striking differences. The average levels of serum cholesterol, esterified cholesterol, neutral fats and total lipids as well as those for serum glucosamine and polysaccharides are somewhat similar in the nondiabetic controls and in the patients with uncomplicated diabetes of similar age. A striking abnormality in both serum lipids and complex carbohydrates is seen in Group IV. The patients of this group show marked elevation of all serum lipid fractions as well as of complex serum carbohydrates. Patients in Group III with early retinopathy without any evidence of renal involvement present apparently statistically significant differences in comparison with patients having uncomplicated diabetes and with nondiabetics. The increases are noted chiefly in neutral fat, total lipids, serum glucosamine, and total serum polysaccharides. In contrast, serum cholesterol and phospholipids remain in normal limits (table 1 and figures 1-4).

DISCUSSION

Although extensive studies of serum cholesterol and lipoproteins have been recently performed in diabetics with and without complications,[3-5] only scant information is available concerning complete serum lipid partitions.[2] Our observations indicate that diabetic patients without complications (Group II) have serum lipid partitions al-

TABLE 1
Summary of chemical data of normal controls, and of diabetics with and without complications

Group	I	II	III	IV
	Normal controls (N)	Uncomplicated diabetes (D)	Diabetes & retinopathy (D_R)	Diabetes & Kimmelstiel-Wilson syndrome (D_{KW})
No. of cases	11	38	12	16
Cholesterol, mg.%				
Total	245±54*	236±49	256±41	318±64
Esterified	----	174±37	187±22	221±59
Phospholipids, mg.%	214±38†	259±47	290±33	326±61
Total lipids, mg.%	629±136†	804±182	958±160	1195±268
Neutral fats,§ mg.%	231	310	411	550
Glucosamine, mg.%	97±8‡	106±16	136±18	168±30
Polysaccharide, mg.%	146±11‡	139±11	158±20	181±23

	Probability values (p)		
	D vs. D_R	D vs. D_{KW}	D_R vs. D_{KW}
Cholesterol, total	0.23	0.0001	0.02
Phospholipids	0.035	0.0001	Not significant by inspection
Total lipids	0.018	0.0001	0.023
Glucosamine	0.0001	0.0001	0.0025
Polysaccharide	0.00015	0.0001	0.013

*Mean values obtained in 73 controls of age 48 to 52 by Boas, Elster and Adlersberg.[16]
†Mean values of 11 healthy men.
‡Mean values obtained in 15 nondiabetic controls by Berkman, Rifkin and Ross.[8]
§Those are calculated figures; no standard deviation is given.

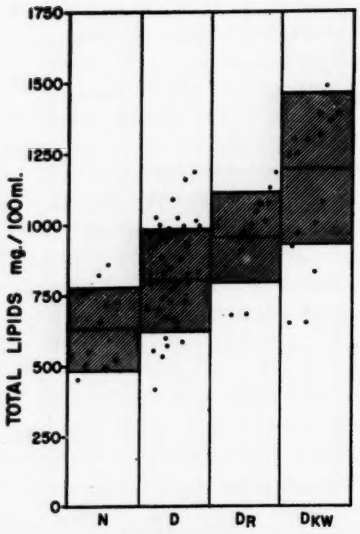

FIG. 1. Serum total lipid (mg. per 100 cc.) in normal controls (N), uncomplicated diabetes (D), diabetes and retinopathy (Dr) and diabetes and Kimmelstiel-Wilson syndrome (Dkw). The interrupted horizontal lines represent the mean of each group and the shaded areas on both sides of the mean represent the standard deviation.

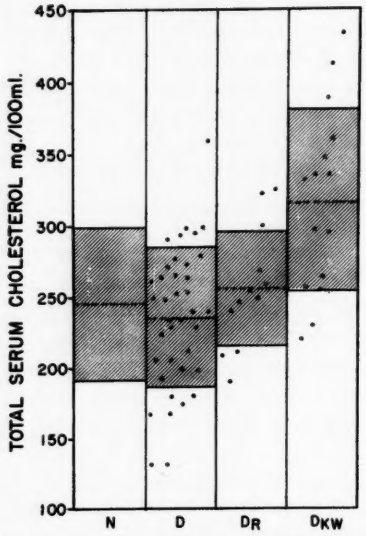

FIG. 2. Total serum cholesterol (mg. per 100 cc.) in the four groups studied. For details see legend to figure 1.

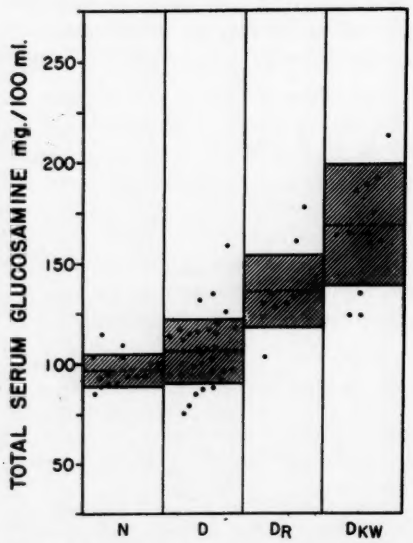

FIG. 3. Serum glucosamine (mg. per 100 cc.) in the four groups studied. For details see legend to figure 1.

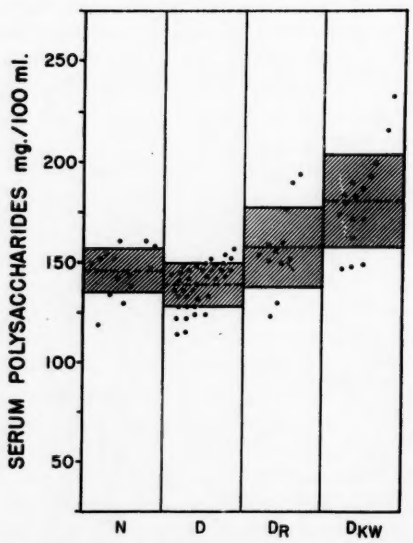

FIG. 4. Serum polysaccharides (mg. per 100 cc.) bound to serum protein in the four groups of persons studied. For details, see legend to figure 1.

most similar to those noted in nondiabetic controls (Group I), except for a slight increase of neutral fats and total lipids. Diabetic patients with early retinopathy (Group III) differ from uncomplicated diabetes (Group II) by significant elevations of serum neutral fats and total lipids without any associated change in serum cholesterol and phospholipids. Keiding *et al.*[4] found a significant correlation between elevated values for the Sf 12 to 20 fraction of lipoproteins and the presence of retinopathy in diabetics. Although there may be pathogenetic

implications, it is difficult to evaluate the marked elevations of all serum lipid fractions in patients with advanced nephropathy (Group IV). These findings may simply reflect profound renal insufficiency or metabolic alteration in the nephrotic syndrome.

As previously observed, the earliest increases of serum glucosamine and polysaccharides are found in diabetic patients with early retinopathy.[8, 9, 21-23] It appears, therefore, that the elevations of both lipids and carbohydrate fractions are found in the earliest clinically detectable specific complications of diabetes mellitus. Although the elevation of serum carbohydrate fractions may be interpreted as a nonspecific index of tissue injury or depolymerization,[7, 24-26] it would be difficult to evaluate the simultaneous increases in serum neutral fat and total lipids in the same light. Although these elevations have been found in diabetic patients with retinopathy,[27, 28] in whom no renal dysfunction exists, it is still possible that more precise evaluation of discrete kidney function would indicate minute functional abnormalities. Preliminary observations by the Montefiore group indicate that this possibility is not a real one.

One must consider, therefore, that the blood changes perhaps precede the degenerative alteration of the tissue and the deposition of protein-carbohydrate and protein-lipid compounds in the retina and in the renal glomerulus. Thus, the increases of serum lipid and carbohydrate components which have been observed may both be pathogenetically related in the development of diabetic retinopathy and diabetic glomerulosclerosis. Whether both the lipids and carbohydrate fractions increase in parallel fashion or one precedes the other remains to be investigated.

SUMMARY

1. Lipid fractions, including cholesterol, phospholipids, total lipids, neutral fats, glucosamine, and total polysaccharides bound to protein, were estimated in 66 patients with and without specific degenerative vascular disease.

2. In patients with uncomplicated diabetes the concentration of these substances in the serum remained within normal limits.

3. Diabetic patients with retinopathy but without evidence of renal involvement showed increases of total serum lipids, neutral fats, glucosamine, and polysaccharides. The serum cholesterol and phospholipids remained within normal limits.

4. Patients with fully developed diabetic glomerulosclerosis (Kimmelstiel-Wilson syndrome) exhibited elevation of all lipid fractions as well as serum glucosamine and polysaccharides.

5. The possible role of these substances in the pathogenesis of diabetic retinopathy and diabetic glomerulosclerosis was discussed.

SUMMARIO IN INTERLINGUA

Seral Lipidos e Polysaccharidos in Diabete Mellite

1. Fractiones lipidic—includente cholesterol, phospholipidos, lipidos total, grassias neutre, glucosamino, e polysaccharidos total ligate a proteina—esseva estimate in 66 patientes con e sin specific morbo vascular degenerative.

2. In patientes con noncomplicate diabete le concentration de iste substantias in le sero remaneva intra limites normal.

3. Patientes diabetic con retinopathia sed sin evidentia de affection renal monstrava augmentos del valores seral total de lipidos, grassia neutre, glucosamino, e polysaccharidos. Le cholesterol e le phospholipidos del sero remaneva intra limites normal.

4. Patientes con perdisveloppate glomerulosclerosis diabetic (syndrome de Kimmelstiel-Wilson) exhibiva elevate nivellos de omne fractiones lipide e etiam del seral glucosamino e polysaccharidos.

5. Es discutite le rolo possibile de iste substantias in le genese de retinopathia diabetic e glomerulosclerosis diabetic.

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DISCUSSION

ARTHUR R. COLWELL, M.D., (*Chicago*): Was there a determination of these substances on only one blood specimen in each patient? Do you know what serial determinations might show on different days or at different times of day? Could you give us any idea of what the relationship of these values was to the state of control of the diabetes in the diabetics?

CHUN-I WANG, M.D., (*New York City*): All determinations were performed simultaneously in fasting blood specimens (groups II-IV). In the nonfasting state the neutral fat content varies with the quantity of dietary fat and the time interval between the last meal and the drawing of blood. On a constant regimen (diet and insulin) the individual lipid fractions remain fairly constant for the same person in the fasting state.

BERNARD A. WATSON, M.D., (*Clifton Springs, New York*): What average diet was given these patients, as far as carbohydrate, protein and fat content is concerned?

DR. WANG: Diabetics with very poor control exhibit marked increases in serum neutral and total fats. It may be stressed that the patients with diabetes included in this study showed adequate control, as may be seen from the presented data.

HAROLD RIFKIN, M.D., (*New York City*): In response to Dr. Colwell, we have measured the serum glucosamine and the total protein-bound polysaccharide serially in a few individuals during a 24-hour period, and there appears to be only slight diurnal variation.

In terms of control, we are a little more disturbed now than we were two years ago. It appears that in some patients who have a very poor level of control, the serum mucopolysaccharides are markedly elevated; then when we controlled them, the polysaccharides became relatively normal. However, the studies presented this morning were based on patients who maintained a fair level of control during the observed period.

Referring to Dr. Watson's question about diet, the carbohydrate intake was in the range of 200-250 gm., protein 70-90 gm., and the rest in fat to make up the necessary caloric intake.

KENNETH STERLING, M.D., (*Syracuse, New York*): I would like to ask either Dr. Wang or Dr. Rifkin whether the reported changes in glucose or polysaccharides have a close relationship to alpha-globulin changes previously reported in diabetic glomerulosclerosis.

DR. RIFKIN: In 1951 Dr. Petermann and I predicted that the highest concentration of carbohydrate would reside in the alpha-2 globulin fraction. Since then, we have measured the carbohydrate concentration of the various protein fractions electrophoretically. I would say, and I believe this is Drs. Keiding's and Tuller's experience in Boston also, that the alpha-2 globulin contains the highest concentration of polysaccharide.

Thrombocytopenic Purpura as a Probable Manifestation of Insulin Allergy

Report of a Case

Georg R. Constam, M.D., Zurich, Switzerland*

Purpura in diabetes has been rarely described. Joslin and co-workers[1] quote two cases without discussing the relationship between diabetes and the blood changes. Kern and Langer[2] report nonthrombocytopenic purpura as an allergic manifestation to insulin and Travia[3] mentions purpura as a manifestation of allergy to insulin therapy.

The observation of a diabetic patient developing severe thrombocytopenic purpura, the probable connection of the latter with insulin, its favorable reaction to ACTH, prednisone and cortisone therapy, and the important value of in vitro tests to recognize allergens, seem of general interest and to justify publication.

CASE REPORT

A 60-year-old foreman was admitted to the Bethanien hospital May 21, 1955, on account of thrombocytopenic purpura and diabetes mellitus.

His family history was irrelevant, except that, 25 years previously, his only son had died at the age of 7 of aplastic anemia.

Twenty years before the present admission, diabetes was discovered and carefully treated by diet alone until 15 years later, when coronary thrombosis lowered the tolerance and insulin therapy had to be instituted. After improvement of his cardiac function, the patient's condition remained very satisfactory with about 20 units of protamine zinc insulin once daily. However, in April 1955, epistaxis developed, gradually becoming more frequent and severe. On May 20th he consulted his family physician,† who made the diagnosis of thrombocytopenic purpura and referred the patient for hospital treatment.

On admission the patient showed an enormous number of small punctate hemorrhages all over the skin, many small hematomas in his gums, throat, palate and tongue. Neither liver nor spleen was enlarged. Blood pressure was 175/80 mm. Hg. Urine contained 42 gm. of glucose in 24 hours, a trace of acetone, a trace of protein; urobilinogen and urobilin were increased. Capillary blood sugar was 305 mg. per cent; hemoglobin, erythrocytes, leucocytes, differential count normal; thrombocytes numbered 27,000 (Fonio's and Babnik's methods), bleeding time was 8½ min., coagulation time 2½ min., prothrombin time 20 sec.; the nonprotein nitrogen 30 mg. per cent.

The bone marrow was, according to Dr. Karl Rohr‡ rather rich in fat, erythroblasts about normal in number with mitotic figures; granulopoesis was normal; megakaryocytes were not decreased, showing basophilia of their cytoplasm and rather young nuclei; there was an increase of plasma cells and reticular elements. The hematologist's conclusion from the increase in plasma and reticular cells and the normal number of megakaryocytes was the presence of a "toxic-allergic" condition.

In order to obtain rapid control of the diabetes, *regular insulin* was substituted for *protamine zinc insulin*. To check the thrombocytopenia, *cortisone* therapy was started immediately after hospital admission. The different drugs used and the most important blood tests are recorded in table 1. The patient's condition improved rapidly. Temperature ranged between 36.4° C on admission and 37° C for the first 12 days, and between 35.8° C and 36.6° C until the 18th day.

Since he had been using protamine zinc insulin for five years without any difficulty and since he had changed neither type nor brand of insulin, it appeared at first very unlikely that insulin could cause the thrombocytopenia. We searched for other substances with benzol-like action, but could not discover any contact with other drugs or related chemical compounds.

Preparing the patient for dismissal from hospital, he was changed from regular to *zinc insulin Semilente*, and on the 18th hospital day, one injection of 26 units was given before breakfast. In the evening the temperature rose to 37.9° C, the platelets had dropped from 60,000 to 40,000, and the patient started to bleed again. This clinical observation roused the suspicion that zinc insulin Semilente might have caused the recurrence. This opinion was fostered when we learned on the same day, that nephelometric examination of the patient's serum when tested with all medications he had received prior to the appearance of thrombocytopenia, showed positive reaction with protamine zinc insulin and with zinc insulin Semilente. That evening *regular insulin* NOVO was used again, but in spite of it, the patient's condition grew rapidly worse. The following morning his temperature rose to 39.7° C, the bleeding from his nose became extremely difficult to control. After 48 hours regular insulin NOVO was re-

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TABLE 1

Date 1955	Insulin	Dosage morning	noon	evening	Platelets	Cortisone mg.	Prednisone mg.	ACTH units	Penicillin units	Antistin
5/21	regular insulin Novo		10	8	22,000	50				300 mg.
5/22	" " "	26	16	30		200				
5/23	" " "	36	16	34	26,000	200				
5/24	" " "	34	16	36		150			300,000	
5/25	" " "	34	20	36	49,000	150			600,000	
5/26	" " "	34	20	24		100			600,000	
5/27	" " "	30	20	26	56,000	100				
5/28	" " "	40	20	26		100				
5/29	" " "	36	20	20		100				
5/30	" " "	36	16	20		100				
5/31	" " "	26	16	20		75				
6/1	" " "	30	16	30	40,000	75				200 mg.
6/2	" " "	36	16	26		50				200 mg.
6/3	" " "	30	20	16		100				200 mg.
6/4	" " "	24	14	14		75				200 mg.
6/5	" " "	30	14	16		100				300 mg.
6/6	" " "	26	16	10	60,000	100				300 mg.
6/7	insulin Novo Semilente	26			40,000	100			600,000	
	regular insulin Novo			14						300 mg.
6/8	" " "	8	4	18	45,000	150			300,000	
6/9	" " "	20	12			200			340,000	
6/9	regular insulin Wellcome			16	34,000					
6/10	" " "	20	16		20,000	200			600,000	
	regular insulin Novo			24						
6/11		0	0	0	10,000, 7,000		40		600,000	200 mg.
					15,000					
6/12	" " "	16	20	20	14,000		10	164	240,000	
6/13	" " "	12	10	20	10,000, 16,000		15	84	480,000	
6/14	" " "	16	20	28	10,000, 16,000		30	56	480,000	
6/15	" " "	30	20	34	22,000		30	80	480,000	
6/16	" " "	28	20	16	42,000		30	60	480,000	
6/17	" " "	26	18	16	54,000		30	40		
6/18	" " "	16	10	10	56,000		30		420,000	
6/19	" " "	10	6	8			15			
6/20	" " "	10	6	6	73,000		15			
6/21	" " "	10	10	8	210,000		5			
6/22	" " "	10	10	8						
6/23	" " "	12	10	8	114,000		20		300,000	
6/24	" " "	12	10	8	60,000		40		300,000	
6/25	" " "	30	16	16	54,000, 60,000		40		300,000	
6/26	" " "	26	16	20		100				
6/27	" " "	28	16	18	70,000	75				
6/28	" " "	26	16	14	83,000	75				
6/29	" " "	28	14	14	76,000	75				
6/30	" " "	22	22	16						
7/1	" " "	16	10		45,000					
7/2	" " "	12	12	10	45,000	125				
7/4	" " "	24	14	16	115,000	125				
7/7	" " "	20	12	10	120,000	100				
7/11	" " "	20	12	10	135,000	75				
7/25	" " "	16	12	8	120,000	75				
8/22	" " "	14	5	8	145,000	25				
9/22	" " "	16	6	8	135,000	37				
10/10	" " "	16	6	8	140,000					
12/11	" " "	16	8	10	140,000					
1/30/56	" " "	20	10	10	180,000					

placed for 24 hours by *regular insulin* (*Wellcome*), then for one day *all insulin was withheld*. These changes plus one transfusion of 250 ml. of fresh whole blood did not help. The patient deteriorated rapidly, his thrombocytes dropped to 9,000 and he started to expectorate and to vomit blood.

At this stage intravenous ACTH therapy was started and continued for six and a half days. Prednisone was given concurrently and for 14 days in varying dosage. The bleeding stopped promptly, but the patient developed a full-moon face, edema and dyspnea. On substituting cortisone for prednisone and ACTH, the retained water was lost rapidly. The general condition of the patient improved so much that he could leave the hospital 12 days after the cessation of ACTH infusions. For almost two months he continued to take

cortisone at home in gradually diminishing dosage, then stopped this therapy, and has continued to use regular insulin and dietary control. The patient is now working normally and feeling fine.

Through the courtesy of Dr. K. Hallas-Møller and J. Schlichtkrull from the Novo Terapeutisk Laboratory in Copenhagen it was possible for Dr. Hoigné* to test the patient's serum with protamine zinc insulin NOVO, zinc insulin NOVO Semilente, insulin NOVO pig glands, zinc insulin NOVO Lente, protamine sulfate, methylparahydroxybenzoate, regular insulin NOVO, crystallized insulin NOVO, insulin NOVO ox glands and procaine. For the detection of the causative allergen, two "in vitro" methods have been used, the "thrombocyte-agglutination test" of Hoigné and Storck[4] and the nephelometric serological method of Hoigné, Grossmann and Storck.[5] Both tests gave a positive result with protamine zinc insulin, insulin Semilente, insulin Lente, insulin NOVO pig glands, protamine sulfate and methylparahydroxybenzoate, a negative result with regular insulin NOVO, crystallized insulin NOVO, insulin NOVO ox glands and procaine. The thrombocyte-Coombs test according to the method of Flückiger, Hässig and Koller[7] and kindly performed by Dr. Flückiger† was negative.

SUMMARY

A diabetic subject is described who, after using protamine zinc insulin for five years, suddenly developed severe thrombocytopenic purpura. Cortisone therapy stopped the bleeding and improved the patient's condition. Following a single dose of zinc insulin Semilente there was a severe recurrence of the purpura with almost fatal outcome. Immediate treatment with ACTH followed by cortisone therapy and avoidance of "in vitro" positive insulins was followed by recovery. The thrombocytopenic purpura in this instance is regarded as an allergic manifestation due to protamine zinc insulin and to zinc insulin, Semilente. "In vitro" tests for the identification of the allergen were positive with the same preparations and support the conclusion that the sudden drop in blood-platelet was due to protamine zinc insulin and insulin Semilente.

SUMMARIO IN INTERLINGUA

Purpura Thrombocytopenic Como Manifestation Probabile de Allergia a Insulina

Es describite un subjecto qui, post haber usate insulina a protamina e zinc durante cinque annos, disveloppava subitaneemente sever purpura thrombocytopenic. Therapia a cortisona arrestava le sanguination e meliorava le condition del patiente. Post un sol dose de insulina Semilente a zinc il habeva un sever recurrentia del purpura con exito quasi mortal. Un immediate tractamento con ACTH sequite per therapia a cortisona e le exclusion de insulinas con reactiones positive in vitro resultava in recovramento. Le purpura thrombocytopenic in iste caso es considerate como un manifestation allergic debite a insulina a protamina e zinc e a insulina Semilente a zinc. Tests in vitro pro le identification del allergeno esseva positive con le mesme preparatos lo que supporta le conclusion que le subitanee reduction del plachettas sanguinee esseva causate per insulina a protamina e zinc e per insulina Semilente.

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Lente Insulin in Diabetic Children

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Lente insulin has been used in the diabetes outpatient clinics of the Children's Memorial Hospital and Evanston Hospital for the past eighteen months. This paper is the first report of our experiences with this new type of insulin.

Since 1922, when insulin was first discovered, many modifications have been tested, and several have been made available for clinical use. No single preparation has been entirely satisfactory, although various combinations have been used with better results. Recently a new modification, Lente insulin, has become available. Developed in the Novo Laboratories in Denmark, it was first described by Hallas-Møller in 1951.[1] Since then a number of reports have indicated that this insulin has a definite place in the treatment of diabetes mellitus.[2, 3, 4, 5, 6]

The production of Lente insulin is based on the recent discovery that insulin together with a small quantity of zinc, the combination precipitated in an amorphous or crystalline state, has a protracted effect. The need for various modifying agents such as protamine, globin, histone and surfen, which are foreign proteins, is not necessary. By using an acetate buffer, instead of the commonly employed phosphate buffer which combines with zinc, and by carefully regulating the *p*H during precipitation, combinations of zinc and insulin can be produced in two different physical forms. The amorphous form, designated Semilente, shows only a slight prolonged action, approximately twelve hours. The crystalline form, designated Ultralente, has a very low solubility and shows a range of activity of more than 30 hours. The zinc content of both preparations is the same as in protamine zinc insulin, 2 mg. per thousand units. The *p*H of the preparation is 7.2. A mixture of these two forms consisting of 70 per cent of the Ultralente and 30 per cent of the Semilente has been designated Lente insulin and has a range of activity of about twenty-four hours. This mixture, which we used in our study, was furnished by the Eli Lilly Company.

The preliminary report by Hallas-Møller[1] indicated that satisfactory control of blood sugar could be obtained in a large number of difficult cases of diabetes mellitus with a single daily injection of an appropriate mixture of Semilente and Ultralente insulins. Peck and Kirtley[2] concluded that the ratio of 30 per cent Semilente to 70 per cent Ultralente was generally most useful; its action was similar to NPH insulin and in occasional cases somewhat longer in duration. Ferguson[3] compared Lente insulin with multiple daily injections of soluble insulin in fifteen diabetic children and found that the control of blood sugar was at least as good with Lente insulin, and in some cases better. He felt that the majority of diabetic children could probably be satisfactorily controlled with the insulin-zinc suspensions. Gurling[4] studied 45 diabetic children, 30 of whom were patients of long standing. Of these 30 patients, 11 showed improvement with the new insulin while the other 19 patients remained unimproved in the control of their diabetes. The other 15 patients were recently diagnosed cases, and all were satisfactorily controlled. Both authors[3, 4] had to vary the percentage of Semilente and Ultralente insulin in the mixtures they used for adequate control of their patients.

The indications for the use of Lente insulin include difficult control with other insulin preparations, requirement of multiple injections, and allergy to other types of insulin.

METHOD OF STUDY

Fifty-four children were studied in private practice and in the diabetes outpatient clinics and hospitals whence

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this paper originates. Fifteen were previously untreated diabetics who were managed with Lente insulin immediately following the treatment of their initial acidosis with crystalline zinc insulin. The other thirty-nine children had diabetes of long duration and showed variable degrees of control prior to their transfer to Lente insulin. None of the children was hospitalized specifically for this study. Only those with complications requiring hospitalization were subjected to laboratory studies other than the simple urine tests for glucose and acetone.

A few of the children received Lente insulin while hospitalized, but the majority received it as a routine procedure in the clinic. The initial dosage was one unit of Lente insulin for each unit of the previous insulin used. In the first few cases, Lente was used alone, but it soon became apparent that crystalline insulin would have to be added in approximately the same amount as was prescribed with NPH insulin. Variations in insulin dosage of a few units were frequently made when indicated but were not felt to be significant. The insulin was given in one daily injection before breakfast. When crystalline insulin was added to the Lente insulin, it was mixed in the same syringe by the patient. The dose of crystalline insulin was small, usually one-fourth of the total, but in a few instances one-half of the total daily insulin was prescribed. In one case it was necessary to mix the insulins in the bottle.

All patients received a weighed diet of approximately 3 to 4 gm. of protein per kilogram of body weight, with a protein to fat to carbohydrate ratio of approximately 1:1:2. The total caloric value was appropriate for their ages and ideal weights. The division of calories among the three main meals was approximately equal and varied only slightly in the individual patients when it seemed that extra food at a particular meal controlled the hypoglycemic tendencies following that meal. The weighed diets were maintained at home and in the hospital with slight variations in the amount of the mid-afternoon and bedtime feedings. A few of the patients also received mid-morning feedings.

The patients were unrestricted in their activity. They were required to test their urine three to five times daily, and to record in a notebook in appropriate colors the presence or absence of glycosuria. In the hospital the patients' urine was checked four times daily, frequent fasting blood sugars were determined, and twenty-four-hour urinary glucose was determined quantitatively. The activity of the hospital patients was unrestricted within the ward but was generally less than at home.

The estimation of clinical control was based on the patient's well-being, freedom from symptoms, and a normal gain in weight. If acetone appeared in the urine, or glycosuria appeared in more than half of the daily urine specimens, or mild reactions occurred, diabetes was considered to be unsatisfactorily controlled and readjustment of the insulin dosage or diet was made. Under the conditions of the study, it was impossible to set up more rigid criteria of satisfactory control. The parents were questioned about the general condition of the child, and their observations were recorded in the patient's chart. This study is based upon these observations. Laboratory studies, other than the simple urine tests for sugar and acetone, were used primarily as an aid to achieving good clinical control.

RESULTS

The ages of the children varied from 15 months to 15 years, the duration of the diabetes from 2 weeks to 8½ years. In nine children NPH insulin was reinstituted for the following indications: Eight children were poorly controlled with Lente insulin. Of this group one father felt that his son's general condition was better with NPH insulin after a one-month trial with Lente insulin. This boy observed no dietary restrictions at home and varied his insulin from one-half to twice the prescribed dosage. Blood glucose determinations while the patient was in the hospital showed much better control with Lente insulin.

The ninth child who was returned to NPH insulin seemed to be doing well with Lente insulin. His weight gain was good and he had less glycosuria. However, after a three-month period his liver became enlarged. The liver function tests were normal except for hypercholesterolemia. One month later, with no decrease in hepatomegaly, NPH insulin was prescribed. There was a recession in liver size after three months.

BRIEF CASE REPORTS

1. J. Z., a girl of five years, entered the Children's Memorial Hospital with diabetic acidosis which responded well to therapy with crystalline insulin and parenteral fluids. She was well controlled in the hospital with Lente insulin and crystalline insulin. However, because of the parents' inability to comprehend the mixing of Lente and crystalline insulin, it is now mixed in the proper proportions in one bottle, as needed. She is gaining weight, and her glycosuria is well controlled.

2. L. S., a Puerto Rican girl of five years, had received an unknown amount and type of insulin prior to her first admission to Children's Memorial Hospital. She weighed 12 kg. and had had symptoms of diabetes for about five months. Her history was obtained through an interpreter and was incomplete. Her mother and maternal grandmother are diabetic. Nineteen units of Lente insulin and 10 units of crystalline insulin were prescribed. Blood glucose determinations at two-hour intervals between 8:30 a.m. and midnight were between 50 and 125 mg. per 100 cc. from noon until midnight, but the mid-morning spe-

cimen was over 400 mg. per 100 cc. This extremely high value was thought to be due to an insufficient amount of crystalline insulin. On the following day, additional crystalline insulin was used with better blood glucose control in the morning. She gained 6 kg. in the next five months.

3. J. H., a boy of nine years, had been managed for four years with a mixture of NPH and crystalline insulin. He was changed to 34 units of Lente insulin without added crystalline insulin seven months ago, and since then his general well-being and control have been better. This child was one of the two patients we were able to manage with Lente insulin alone.

Of the 15 previously untreated patients, 14 have been managed with a mixture of Lente insulin and crystalline insulin following the treatment of their initial acidosis with crystalline insulin. The other one, an 11-year-old girl, had been satisfactorily controlled on 32 units of Lente insulin alone. She has gained 4 kg. Control of all the new diabetics has been very satisfactory in spite of difficult home situations in two instances.

DISCUSSION

Our observations of 54 juvenile diabetic patients over a period of 18 months has shown that Lente insulin appears to be an effective and reliable intermediate-acting insulin preparation for the treatment of diabetes mellitus in children. Its time and mode of action are very similar to those of NPH insulin, but in some cases somewhat longer in duration. When a patient has been well controlled on NPH insulin, the transition to Lente insulin on a unit for unit basis is usually smooth.

In most patients, we found it necessary to add some crystalline zinc insulin to the Lente insulin to achieve adequate control. The two insulins were then mixed in the same syringe. The difference in *p*H of the two preparations seemed to cause no noticeable alteration in the time action of the Lente insulin other than what would be expected by the addition of crystalline insulin. Mixtures with approximately 40 per cent Semilente insulin and 60 per cent Ultralente insulin may more nearly approximate the needs of most diabetic children.

The specific advantages of this new insulin preparation as compared to NPH insulin are the absence of a foreign protein and a slightly longer duration of action. The stinging sensation noted in about 20 per cent of our patients is a minor disadvantage. Another disadvantage of the Lente insulin is the occurrence of more frequent early morning reactions which may be overcome by careful prescription of the bedtime feeding or reduction of the dose of Lente insulin.

Indications

We have prescribed Lente insulin for all new diabetic patients, for all whose matutinal glycosuria has not been satisfactory, and for all poorly controlled "brittle" diabetics.

Unusual Reactions

Patients who had repeated severe hypoglycemic reactions are likely to have similar episodes with the new insulins and are particularly to be cautioned concerning the probable timing of hypoglycemic episodes. Severe hypoglycemic episodes have been observed under a variety of circumstances, including change from daylight saving time to standard time, later breakfast on Sunday after an active week end, and change to Lente insulin. For example, a 13-year-old girl who was poorly controlled on various mixtures of 120 units of insulin, had 2 severe reactions with Lente insulin until her new insulin requirement was found to be 80 units. Another girl developed hives which disappeared when NPH insulin was prescribed. Infants and children up to five years of age have been less well controlled and have appeared to have more frequent insulin reactions with Lente insulin.

SUMMARY

Fifty-four diabetic children were studied in hospitals and out-patient clinics and in private practice. With a weighed diet and unrestricted activity, their level of control was estimated on subjective and objective evidence. Of the 39 previously diagnosed and treated juvenile diabetics, 24 were improved with Lente insulin, 6 showed no change, and 9 were returned to their former type of insulin. The 15 newly discovered diabetic patients were satisfactorily controlled with Lente insulin.

The change to the new insulin was usually uncomplicated, and alteration of dosage was insignificant. Hepatomegaly developed in one patient and urticaria in another, but both conditions receded when NPH insulin was reinstituted.

Lente insulin is an effective and reliable intermediate-acting insulin preparation for the treatment of juvenile diabetes mellitus. Its time and mode of action are very similar to those of NPH insulin but in some cases somewhat longer in duration. When a patient has been well controlled with NPH insulin, the transition to Lente insulin on a unit for unit basis is usually smooth. In most patients it is necessary to add some crystalline zinc insulin to the Lente insulin to achieve adequate control.

SUMMARIO IN INTERLINGUA

Insulina Lente in Diabeticos Juvenil

Esseva studiate 54 diabeticos juvenil in hospitales, clinicas a patientes visitante, e le practica private. Con dietas a peso determinate e sin restriction del activitate, lor grados de controlo del morbo esseva estimate super

le base de datos subjective e objective. Le gruppo includeva 39 diabeticos juvenil qui habeva essite diagnosticate e tractate ante le tempore del presente studio. Inter illes, 24 esseva meliorate per insulina Lente, 6 monstrava nulle alteration, e 9 esseva retornate a lor previe typo de insulina. Le 15 novemente discoperite casos, etiam includite in le serie total, attingeva satisfacente grados de controlo del morbo per medio de administrationes de insulina Lente.

Le transition al nove typo de insulina causava generalmente nulle complication. Le alteration del dosage non esseva significative. Hepatomegalia se disveloppava in un patiente e urticaria in un altere, sed ambe iste conditiones dispareva quando insulina NPH-50 esseva reinstituite.

In le tractamento de patientes juvenil de diabete mellite, insulina Lente es un efficace preparato a action intermediari. Su tempore e su modo de action es similissime a illos de insulina NPH-50, sed in certe casos insulina Lente ha un durantia plus extense. In le caso de patientes qui ha attingite bon grados de controlo per medio de insulina NPH-50, le transition a insulina Lente in dosages identic es generalmente libere de complicationes. In le majoritate del casos il es necessari adder al insulina Lente un pauco de crystallin insulina a zinc pro obtener adequate grados de controlo.

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Vitamin B_{12} Deficiency in Vegetarians

Children appear to be more adversely affected by the (vegetarian) diet than adults, and Wokes *et al.* suggest that the absence of symptoms in the group of American vegans studied by Hardinge and Stare may be because the British group contained more young people "who are probably more susceptible to vitamin B_{12} deficiency." That a vitamin B_{12} deficiency was involved was suggested by the serum of vitamin B_{12} levels. These ranged from 45 to 193 micromicrograms per milliliter (average 111 micromicrograms per milliliter) as compared with the average normal range of 200 to 300 micromicrograms per milliliter, and in more than half the vegans the average concentration was less than 120 micromicrograms per milliliter. Further, the deficiency symptoms in vegans could be alleviated by administration of vitamin B_{12}, and one of the investigators (J. Badenoch) has described [*Proc. Roy. Soc. Med.* 47:426 (1954)] the case of a vegan boy, age 15, who developed a severe vitamin B_{12} deficiency with subacute combined degeneration of the cord which "responded dramatically" to treatment with vitamin B_{12} alone. Some support for these findings of vitamin B_{12} deficiency in vegans is provided by a Dutch study [W. F. Donath, I. A. Fischer, H. C. van der Meulen-van Eysbergen, and J. F. de Wijn, *Voeding* 14:153 (1953)] of 59 adult vegans, 12 per cent of whom developed oral symptoms, and 6 per cent paresthesia. Wokes and co-workers believe that the lower incidence of symptoms "was probably because 72 per cent of the Dutch vegans . . . had been on the vegan diet for less than two years, as compared with an average of five to six years for British vegans."

It is perhaps not surprising to find symptoms of vitamin B_{12} deficiency occurring in people who have been subsisting for years on the vegan diet which, of course, contains no animal protein.

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Ocular Nerve Palsies with Headache in Diabetes Mellitus

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Isolated cranial nerve lesions are reported as occurring with greater frequency in patients suffering from diabetes mellitus than in a nondiabetic population.[1] Cranial nerves III and VI appear to be involved most frequently, and not VII as stated by Joslin *et al.*[2]

The association of severe headache or periorbital pain with the ocular nerve palsies in diabetic subjects appears to have escaped attention until the recent report by Jackson.[3] The possibility of an accompanying trigeminal neuritis is mentioned by Martin[4] and Goodman *et al.*[5]

The three cases reported here illustrate association of unilateral headache and ocular nerve paresis; they form part of a small series of six patients with ophthalmoplegias seen in this clinic in the last five years.

CASE REPORTS

Case 1. A man aged 59, known to have had diabetes for 24 years, was admitted because of frontal headaches of recent onset. His diabetes was inadequately controlled on 40 units of an insulin mixture daily. The past medical history was noncontributory, and there was no evidence of alcoholism. Neurological examination revealed absence of knee and ankle jerks and loss of vibration sense at the ankles. The blood pressure was 120/80.

Within a few days of admission he developed diplopia, and his headache increased in severity, becoming localized over the left eye. Examination revealed left sixth nerve palsy which became complete over a period of about 48 hours. During the following week he developed a right sixth nerve palsy which was also gradual in onset. There was no objective evidence of involvement of the trigeminal nerve, although the distribution of pain strongly suggested this. Radiographs of the skull and sinuses and air encephalography were normal. The cerebrospinal fluid was normal, and the Wassermann reaction was negative in both blood and cerebrospinal fluid. Tests for sweat secretion showed loss of sweating over the lower extremities, and a cystometrogram showed a "pseudotabetic" curve as seen in diabetic patients with autonomic neuropathy. Both of the ocular palsies disappeared within three months without specific therapy other than the control of his diabetes.

Case 2. A woman 61 years of age, diabetic for the previous 6 years, was admitted with a history of 3 days of severe left frontal headache and diplopia. She complained also of pain down the left arm. Her diabetes was moderately controlled on 70 units of zinc protamine insulin daily. There was nothing significant in her past medical history, and she took no alcohol.

Examination showed complete sixth nerve paralysis on the right side, with ipsolateral loss of corneal reflex. There was wasting and tenderness of the left deltoid and triceps muscles and loss of the left triceps jerk. The blood pressure was 200/110, and there was cardiomegaly.

Investigations which included radiographs of the skull and examination of the cerebrospinal fluid were normal. The Wassermann reaction was negative in the cerebrospinal fluid and blood.

Recovery from both headache and diplopia was complete within three months, and there has been no recurrence in the last two years. Treatment was confined to the stabilization of her diabetes.

Case 3. A man aged 68 was known to have had diabetes for 14 years. His diabetes was indifferently controlled on about 24 units of protamine zinc insulin daily. He was also known to have had peripheral neuritis with left foot drop, and he suffered from intermittent attacks of nocturnal diarrhea with rectal incontinence. He had had no other significant illness, and his alcohol consumption was minimal.

In 1954 he was admitted complaining of diplopia and severe pain around the left eye. Examination revealed left third nerve palsy with ptosis, diminished left corneal reflex, and impairment of sensation to light touch over the first sensory division of the left trigeminal nerve. The ankle jerks were absent, and there was loss of sweating over both legs below the knee. The blood pressure was 130/80.

Radiographs of the skull and sinuses were normal; the cerebrospinal fluid was normal. The Wassermann reaction was negative in both cerebrospinal fluid and blood.

Insulin dosage was adjusted to improve diabetic control, but no other treatment was instituted.

Recovery began within three weeks, and was complete at the end of four months. There has been no recurrence.

DISCUSSION

There is still little agreement on the etiology of cranial nerve lesions which occur in diabetic subjects. Collier,[6] reporting the largest series at that time, considered these lesions to be of vascular origin because his patients were mostly in the latter half of life. Weinstein and Dolger[7] considered that the most likely cause of paresis of the extra-ocular muscles was hemorrhage into the ocular nerve nuclei. It seems possible to challenge this view on the following grounds. Ocular nerve palsies have been reported in young subjects with severe diabetes where there was little evidence of vascular degeneration.[8] Further, multiple and recurrent cranial nerve palsies associated with severe and labile diabetes,[9] and the associa-

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tion of a trigeminal nerve lesion suggest a process involving the peripheral nerves rather than the nuclei. Furthermore, the onset is not invariably sudden as would be expected if the cause were always vascular. This point is particularly well illustrated by the patient in Case 1 who was under observation in hospital when his ocular nerve palsies occurred. In this instance it was possible to observe the gradual and progressive development of both sixth nerve lesions.

The neurologic investigations performed in this group, except for Case 1, were limited, but extensive investigations were not thought to be indicated in these cases since the prognosis is known to be good. Therefore, although vascular and space-taking lesions cannot be said to have been excluded, the clinical course did not suggest the presence of such lesions. This small series demonstrates that the ocular nerve palsies of diabetes mellitus may be gradual in onset, and that there may be evidence of an associated trigeminal nerve involvement. This supports the view that they may be "neuritic" in nature and not, as has been previously asserted, always of vascular origin. It is notable that in all three cases there was evidence of peripheral or autonomic neuropathy, either accompanying the ocular nerve lesions or in the past. This association of cranial and peripheral neuropathy was observed by Root.[10]

SUMMARY

The association of unilateral headaches, presumed to be due to trigeminal nerve involvement with ocular nerve palsies, in patients with diabetes mellitus is described. In one the ocular palsies were of gradual onset suggesting a "neuritic" rather than a vascular pathology. Experience suggests that this is not an uncommon pattern of cranial nerve lesions in diabetic patients.

SUMMARIO IN INTERLINGUA

Paralyses del Nervo Ocular con Mal de Capite in Diabete Mellite

Es describite le occurrentia, in patientes de diabete mellite, del association de unilatere mal de capite—supponitemente debite al affection del nervo trigemine—con paralyses del nervo ocular. In un caso le paralyses ocular esseva characterisate per un declaration gradual, lo que pareva indicar un pathologia "neuritic" plus tosto que vascular. Experientias passate indica que iste manifestation de lesiones cranio-nerval non es incommun in patientes diabetic.

ACKNOWLEDGMENT

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Glycosuria, Family History of Diabetes, and Life Insurance

Recent Insurance Mortality Experience

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Detection of diabetes has been a primary aim of this Association ever since its founding. The life insurance business has had a similar interest, and for a much longer time. Although the objective has been different, the detection of diabetes as a result of examination for life insurance has served in some degree a major objective of this Association, namely, to bring diabetics under treatment soon after onset and before the development of symptoms. These diabetics otherwise might have gone undetected until their condition had greatly deteriorated and serious complications ensued. This is by no means a matter of purely academic interest. Urinary examinations in connection with life insurance are very common, and until the rapid expansion of industrial medical examinations in the past decade, they probably constituted the largest proportion of such examinations in apparently healthy people. In the experience of the Joslin Clinic, more than one-fifth of the male patients at ages 35-54 prior to 1930 had their disease disclosed originally as a result of life insurance examination. Even within the last decade, the proportion has been still sizable.[1] Moreover, early discovery of diabetes in this manner has been of benefit. This is shown by the lower mortality among such cases as compared with the general mortality of diabetics of corresponding ages.[2]

The interest of the life insurance business in detecting diabetes has been of significance to clinical medicine in other ways. It has been an important factor in the development and standardization of tests for urinary glucose and blood sugar.[3]

Over the years, a very considerable literature has accumulated on glycosuria among applicants for life insurance. Studies of the mortality among such persons have been made on both individual company[3a] and intercompany experiences.[4, 5, 6] The latter appear in reports of investigations which include a large number of impairment classes. The purposes, characteristics and limitations of these life insurance studies of impaired lives have been summarized by Lew,[7] and only the salient features will be presented here. Most of the present paper relates to the findings of the "1951 Impairment Study,"[6] the latest intercompany investigation. This study was prepared by the Society of Actuaries in consultation with The Association of Life Insurance Medical Directors of America. It covered the experience of 27 life insurance companies in the United States and Canada which have about 70 per cent of all the "Ordinary" insurance outstanding in the two countries. The study relates to persons insured between 1935 and 1949, who were traced to their policy anniversary in 1950. Applicants with serious unrelated impairments, or histories of disease, were excluded to eliminate these extraneous factors. The study was based on applicants accepted for "Ordinary" insurance (insurance issued to individuals in amounts of $1,000 or more), either at regular rates of premium (standard risks) or with some increase over the regular premium rate (substandard risks). These applicants were all medically examined. In some instances, there was more than one examination, or supplementary information was obtained from the applicant's physician.

The findings in these studies are presented in the form of mortality ratios, which are expressed as a percentage of actual to expected deaths. This ratio relates the number of deaths that occurred in a specific category to the number that would have occurred if the mortality had been the same by age at issue and duration of insurance as that experienced by all persons insured, after medical examination, under standard "Ordinary" policies during the same period. Thus, a ratio of 100 per cent means that the mortality experienced is equal to that among standard "Ordinary" risks of the same age who had been medically examined, and observed over the same period of time. For convenience, the term "normal" will be used in this sense.

Presented at the Fifteenth Annual Meeting of the American Diabetes Association in Atlantic City on June 5, 1955.

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These mortality ratios are subject to the same limitation as most statistical observations which are based on samples of limited size. Consequently, the range of probable deviation of the "true" mortality ratio from the observed mortality ratio was calculated in each instance. The range of probable deviation in these cases means that there is an even chance that the "true" value of the mortality ratio lies within the range indicated. The statements made with regard to the significance of the ratios take into account their range of probable deviation.

In interpreting the findings, certain facts should be kept in mind. The death rates of all persons insured under standard "Ordinary" policies during the period covered by the investigation were quite low. Consequently, the mortality standard used to measure the results is quite rigorous. For example, even in the sixth to tenth policy years, the death rates were between only one and slightly over two per 1,000 a year at issue ages under 35, and were at about this level in the eleventh to the fifteenth policy years at issue ages under 30. These death rates thus apply to attained ages up to 45.

Also, during the period covered by the investigation the diseases of the heart and circulatory system came to dominate the mortality picture, followed by malignant neoplasms and accidents in that order. The death rates from diabetes, tuberculosis, pneumonia and influenza, and nephritis were very low, so that a significant excess mortality from any of these causes was generally limited to impairment classifications with a large volume of material. For example, more than 5 deaths from diabetes could be expected only in impairment classifications with more than 500 expected deaths from all causes.

These studies based upon insured lives have certain limitations. For example, applicants are selected on the basis of their acceptability for "Ordinary" life insurance, which presumes a reasonably good state of health when the insurance is issued. On the other hand, the examinations for life insurance are not as thorough as in clinical practice, and the statements of an applicant for life insurance regarding his medical history may not be as complete and frank as those given to his private physician.

PERSONS WITH GLYCOSURIA

The cases included in the "1951 Impairment Study" because of glycosuria totaled close to 10,000. These were subdivided according to the amount and persistency of sugar in the urine, separately for those in which a blood sugar test was made and for those in which this test was not made or was not known to have been made. The experience on cases insured at standard premium rates and on those at substandard premium rates were studied separately. In some classifications the contributing companies were asked to furnish data on substandard cases only. Contrary to what might have been expected, more than 90 per cent of the cases of glycosuria were males. This proportion is significantly larger than in the study as a whole, which averaged approximately 80 per cent males and 20 per cent females. The larger proportion of males in the glycosuria classifications may reflect the higher average age of male applicants and perhaps also the greater frequency with which more than one urine specimen is required on males because they apply more frequently for insurance in large amounts. Some indication of this is seen in the fact that males accounted for more than 95 per cent of the cases with blood sugar tests.

The classifications of glycosuria used in the investigation are shown in table 1. They are affected by the differences between companies in laboratory technics for the determination of the amount of sugar in the urine and in recording its amount. The differences in technics affected both the amount and the persistency of sugar reported. Thus, in the combined experience under the standard section of the glycosuria classifications, more than one-half of the volume of data was contributed by the companies reporting the average amount of sugar in all specimens examined. Most of the remainder was equally divided between companies reporting the average amount in positive specimens only and those reporting the largest amount. In the combined experience under the substandard section, more than half of the volume of data was contributed by companies reporting the average amount in all specimens and about a third by companies reporting the average amount in positive specimens only. Consequently, these classifications by amount and persistency are not so significant as they

TABLE 1

Class of cases with glycosuria used in **1951 Impairment Study**

Accidental	1 test only or no details 1 out of 3 or 4 tests 2 out of 6 or 7 tests
Less than 1%	
Intermittent	1 out of 2 tests 2 out of 3-5 tests 3 out of 6 or 7 tests
Less than 1/2%	
From 1/2% to 1%	
Persistent	2 out of 2 tests 3 out of 3-5 tests
Less than 1/2%	
From 1/2% to 1%	
Over 1%, or history of diet or treatment	

otherwise might have been.

The volume of data in the several classifications varied considerably. In part this reflects the differences in technics described above and differences in the underwriting rules of the individual companies as regards the number of specimens required for rating risks with glycosuria. The number might be less if the applicant had a prior history of glycosuria; perhaps only one specimen would be asked for in the circumstances and the case would be classified as accidental by some companies.

The cases with blood sugar tests were not analyzed according to the levels of blood sugar found, but the blood sugar level would be reflected in the rating of the individual risk. However, in the period covered by this study only those with borderline elevated blood sugar were accepted for substandard insurance, and those with definitely high levels, in the probable diabetic range, were rejected altogether.

The mortality data are shown in table 2 for the larger experience on cases in which blood sugar tests were not made, or were not known to have been made. In the cases insured at standard premium rates, the experience is limited to those with accidental glycosuria or with intermittent glycosuria of 1 per cent or less. The mortality in those with accidental glycosuria was virtually normal. In those with intermittent glycosuria of less than 0.5 per cent, it was slightly elevated. The experience on cases with intermittent glycosuria of larger amount was too small to yield information of value.

In the experience on substandard cases the mortality was significantly elevated over normal in every classification. When account is taken of the size of the experience in the several classifications, by amount and persistency of glycosuria, the differences in the mortality ratios are, for the most part, not statistically significant.

Table 3 gives the facts on cases in which a blood sugar test was made. Those with accidental glycosuria insured at standard premium rates had a mortality virtually equal to the expected. The mortality was only slightly elevated in those with intermittent glycosuria of less than 0.5 per cent.

TABLE 2

Mortality ratios among cases with glycosuria who were not given blood sugar test
By persistency and amount of glycosuria
(1951 Impairment Study)

Classification of glycosuria	Standard Risks		Substandard Risks	
	Claims (no.)	Mortality ratio	Claims (no.)	Mortality ratio
"Accidental"	68	108% ±9	51	165% ±15
Intermittent				
Less than 1/2%	69	126% ±10	22	159% $^{+29}_{-24}$
1/2% to 1%	–	–	12	173% $^{+46}_{-36}$
Persistent				
Less than 1/2%	–	–	20	191% $^{+37}_{-30}$
1/2% to 1%	–	–	11	229% $^{+65}_{-49}$
Over 1%	–	–	8	159% $^{+56}_{-41}$

TABLE 3

Mortality ratios among cases with glycosuria who were given blood sugar test
By persistency and amount of glycosuria
(1951 Impairment Study)

Classification of glycosuria	Standard Risks		Substandard Risks	
	Claims (no.)	Mortality ratio	Claims (no.)	Mortality ratio
"Accidental"	35	95% $^{+13}_{-11}$	29	155% $^{+24}_{-20}$
Intermittent				
Less than 1/2%	22	115% $^{+21}_{-17}$	–	–
1/2% to 1%	–	–	12	168% $^{+45}_{-35}$
Over 1%	–	–	37	134% $^{+18}_{-15}$

In the substandard cases there was a sizable experience only for those with accidental glycosuria, and for those with over 1 per cent of glycosuria. In both instances, the mortality was moderately in excess of the average for all standard risks. The smaller experience on cases with intermittent glycosuria of 0.5 to 1 per cent showed an even higher mortality. While at a casual glance these findings appear to be contradictory, this reflects primarily the technical differences in determining and recording the amount of sugar in the urine, referred to earlier in the paper.

The results are next considered for certain combinations of the data, namely, cases with 1 per cent or less glycosuria, classified according to persistency (table 4). In the experience with cases where a blood sugar test was not made or not known to be made, the mortality was slightly elevated among standard risks with intermittent glycosuria. The mortality in the corresponding substandard experience was more than 1½ times normal. In cases with persistent glycosuria, for which only data on substandard risks are available, the mortality was still higher—twice the expected.

In cases with a blood sugar test, the mortality was also

TABLE 4

Mortality ratios among cases with intermittent or persistent glycosuria of 1% or less
Experience on cases with no blood sugar test and with blood sugar test separately
(1951 Impairment Study)

Classification	Standard Risks Claims (no.)	Standard Risks Mortality ratio	Substandard Risks Claims (no.)	Substandard Risks Mortality ratio
No Blood Sugar Test				
Intermittent glycosuria	75	121% ±9	34	163% $^{+23}_{-20}$
Persistent glycosuria	–	–	31	203% $^{+30}_{-25}$
Blood Sugar Test				
Intermittent glycosuria	26	116% $^{+19}_{-16}$	16	133% $^{+30}_{-24}$

slightly elevated in standard risks with intermittent glycosuria. The ratio was a little, but not significantly higher in the corresponding group of substandard risks.

Certain consistent findings emerge from these figures. The experience on cases with a blood sugar test was slightly but consistently better than in those where the test was not done or there was no information on the matter. On the whole there is indication that the blood sugar test was effective in detecting cases with hyperglycemia. Another factor is that cases given a blood sugar test include an above-normal proportion of applicants for larger amounts of insurance among whom the level of mortality has been found to be generally somewhat lower than among persons insured for smaller amounts.[8]

There is also indication that the mortality is higher in those with larger amounts of sugar in the urine or with more persistent glycosuria as compared with those with accidental or smaller amounts of glycosuria, although results are obscured partly by the differences in technics and recording, and also as would be expected, by the more rigorous selection of the cases with persistent glycosuria of large amount.

The volume of the experience in the individual classifications was not sufficient to disclose significant variations in the mortality ratios by age at issue or by duration. In the combined classifications under the standard sections there was no distinct trend in the ratios, either by age or duration. In the combined experience under the substandard sections, the mortality ratio for issue ages under 40 was virtually normal—103 per cent, but for issue ages 40 and over it was significantly higher—172 per cent. There was no distinct trend in the mortality by duration.

Analysis was made of the causes of death among these glycosurics, but the number of deaths in detailed classifications by amount and persistency of glycosuria was generally small. Accordingly, the facts are presented only for broad combinations of the glycosuria classifications. In the entire standard experience, diabetes accounted for 5 death claims on 4 lives, where only 1.45 claims were expected. This is significantly above normal. The contrast is even greater in the substandard experience where there were 11 death claims from diabetes on 8 lives as against only .88 claims expected. Deaths charged to diabetes comprise a minor fraction of the total mortality—about 3 per cent of all the deaths in the standard experience, and 5 per cent in the substandard experience. However, in view of the association between diabetes and early onset of arteriosclerosis, it may be noteworthy that the mortality from disease of the heart and circulatory system was significantly above normal in several of the substandard classifications.

GLYCOSURIA IN RELATION TO BLOOD SUGAR LEVEL

Mortality data among persons with glycosuria who were given a blood sugar tolerance test are available from an earlier study of the Metropolitan's experience reported by Jimenis, Marks, Finegan and Blatherwick[9] in 1947, which was concerned mainly with the variations in mortality according to blood sugar level. Not all the persons had glycosuria on the examination which brought them into the study, although most of them did or else had a history of glycosuria. Table 5 shows the classification of the cases according to the ½-hour and 2-hour blood sugar levels, based upon determinations of samples of capillary blood by the Folin-Malmros method. Table 6 shows the mortality experience in three broad blood sugar groups according to the amount of sugar in the urine. From this it can be seen at a glance that the mortality was primarily influenced by the blood sugar level. The findings with respect to glycosuria were rather

TABLE 5

Classifications by blood sugar levels of cases given glucose tolerance test
Experience of Metropolitan Life Insurance Company, 1927-1946

	Blood Sugar (Mg. per 100 cc.) ½ hour	2 hour
Normal	200 or less	120 or less
Borderline	201 or more	120 or less
	200 or less	121 to 140
High	201 or more	121 to 140
	Any amount	141 or over

Note: The ½-hour and 2-hour blood sugar values are considered together in classifying the results of the test.

TABLE 6

Mortality ratios among cases given glucose tolerance test according to level of blood sugar and amount of glycosuria

Experience of Metropolitan Life Insurance Company, Ordinary Department Cases examined in 1927 to 1944, traced to anniversary in 1946

	Amount of Glycosuria					
	Less than 0.4%		0.4% but less than 1%		1% or over	
Blood sugar group	Actual deaths	Per cent actual of expected	Actual deaths	Per cent actual of expected	Actual deaths	Per cent actual of expected
Normal	95	108	30	122	21	95
Borderline	23	166	10	127	7	80
High	15	152	6	87	37	189

inconsistent, except where the blood sugar level also was distinctly high.

The findings with respect to hyperglycemia with no or slight glycosuria are in accord with those reported recently by McCullagh and his associates[10] on a follow-up of patients of the Cleveland Clinic who were suspected of having diabetes by virtue of an abnormally elevated blood sugar only, and who otherwise would not have been suspected, since glycosuria was absent. They found that the proportion of patients developing overt diabetes was definitely related to the level of the blood sugar at initial observation. Despite the marked differences between the two studies in the type and source of material and the methods of analysis, they supplement each other well.

FAMILY HISTORY OF DIABETES, ONE OR MORE CASES IN THE FAMILY

From the point of view of volume of experience this is the largest classification in the "1951 Impairment Study." It consisted of those insured who had at least one close relative with diabetes. There were nearly 90,000 cases in this classification, 98 per cent of them in the standard section. The distribution by sex was almost exactly that found among all classes combined in the "1951 Impairment Study"—81 per cent were males, 19 per cent females.

Table 7 shows the mortality experience in the standard section according to age at issue and according to the duration of insurance. There are no significant deviations from the mortality experience among standard risks in general among these cases either by age or by time elapsed from the time insurance was issued. There was a slight downward trend in the mortality ratios with advancing age at issue, but despite the large experience this was not statistically significant.

Further breakdown of the figures among standard risks according to age and duration of insurance from

TABLE 7

Mortality ratios among cases with a family history of diabetes
(One or more immediate relatives)
Experience by age at issue and by duration of insurance separately
(1951 Impairment Study)

	Standard Risks				
Ages at issue	Claims (no.)	Mortality ratio	Policy year durations	Claims (no.)	Mortality ratio
15-64	2,095	100%	1-15	2,095	100%
15-29	184	107%	1- 2	305	103%
30-39	540	105%	3- 5	517	94%
40-49	810	100%	6-10	836	102%
50-64	561	96%	11-15	437	105%

issue was also made. The mortality ratios in these divisions are shown in table 8. By and large the deviations from normal mortality are no greater than might be expected in an experience of this kind. It will be observed that the mortality ratios show a moderate excess over normal in the 11th to 15th policy years among those under 40 when insured. Not much stress can be put on this finding, although the attained ages of these persons lie in the period of life in which diabetes is of sizable frequency.

The mortality from diabetes was significantly high—more than twice the expected at issue ages under 40 and one and two-thirds the expected at ages 40 and over. The total number of claims from the disease was 28, (on 26 lives) or only about 1.5 per cent of the total from all causes. Mortality from nephritis and from diseases of the heart and circulatory system were all significantly high at ages under 40—almost twice the expected from nephritis, and one and one-fifth the ex-

TABLE 8

Mortality ratios among cases with a family history of diabetes
(One or more immediate relatives)
By age at issue according to duration of insurance
(1951 Impairment Study)

	Standard Risks			
	Mortality Ratio			
Ages at issue	Policy year durations 1-2	3-5	6-10	11-15
15-29	89%	117%	99%	127%
30-39	92%	98%	106%	118%
40-49	118%	97%	100%	91%
50-64	97%	83%	99%	107%
	Number of Claims			
15-29	29	55	63	37
30-39	65	121	220	134
40-49	127	200	324	159
50-64	85	143	227	106

pected from diseases of the heart and circulatory system. Mortality for these conditions at ages 40 and over, however, was normal.

Earlier insurance studies have included the mortality experience among persons who reported at least two diabetic relatives at the time insurance was applied for. The number of cases included in two intercompany investigations—the Impairment Study—1938[11] and the Medical Impairment Study—1929[5] was not large, but in both the mortality among such insured persons was about ⅓ higher than normal. The total number of deaths in these two studies was too few to show any significant difference in the mortality from diabetes as compared with average risks.

SUMMARY

A. Long-term follow-up experience on a large number of persons with glycosuria accepted for "Ordinary" insurance shows that: (1) Cases found acceptable for standard insurance have a mortality little different from normal; (2) those limited to substandard insurance because of this impairment have a mortality significantly above normal. This difference primarily reflects the higher proportion in the substandard group of cases with a persistent glycosuria or with large amounts of sugar in the urine; (3) glucose tolerance tests serve to screen out some diabetics, with the result that the mortality among glycosurics having this test was uniformly somewhat lower than among those not having the test; and (4) hyperglycemia is of greater significance than glycosuria in relation to the mortality experienced.

B. A very extensive experience on persons who reported one close relative with diabetes at the time they were insured, showed normal mortality from all causes combined. There was some increase in mortality from diabetes, and, in those under 40, increased mortality from cardiovascular-renal diseases. Earlier studies, based upon applicants with at least two diabetic relatives, showed that they had a moderate increase in mortality above normal from all causes combined.

CONCLUSION

The results of a long-term study of glycosuria in insured persons indicate that generally those with "accidental" glycosuria—that is, found on an occasional specimen—have a favorable prognosis, and even in those with more persistent glycosuria, not clearly diabetic, longevity is not greatly affected. The proportion progressing to diabetes apparently is not large, as judged either by the total mortality or that from diabetes. It is likely that some of these were diabetic at time of application for insurance, but were not detected by the examination for life insurance.

Taken as a whole, persons who are themselves not diabetic but who have a close relative with diabetes, showed no significant diminution of longevity although the frequency with which diabetes subsequently developed among them is above normal.

SUMMARIO IN INTERLINGUA

Glycosuria e Historia Familial de Diabete in Relation al Assecurantia de Vita: Recente Datos de Mortalitate in le Statistica del Assecurantia

A. Le sequente observationes se basa super le analyse statistic del historia assecurantial de grande numeros de individuos con glycosuria a qui polissas "ordinari" habeva essite accordate in le curso de longe periodos de tempore. (1) Individuos classificate como assecurabile sub conditiones standard ha un mortalitate non multo differente ab le norma. (2) Individuos restringite a conditiones substandard de assecurantia a causa de lor glycosuria ha un mortalitate significativemente supranormal. Iste differentia reflecte principalmente le facto que le gruppo a conditiones substandard de assecurantia include un plus alte proportion de individuos con formas persistente de glycosuria o con grande quantitates de sucro in le urina. (3) Tests de tolerantia a glucosa servi a eliminar un certe numero de diabeticos. Isto explica le observation constante que le mortalitate es levemente plus basse inter glycosuricos pro qui tests del tolerantia a glucosa esseva executate que inter glycosuricos pro qui ille tests habeva essite omittite. (4) In relation al mortalitate del gruppo de individuos studiate, le presentia de hyperglycemia es plus significative que le presentia de glycosuria.

B. Le analyse statistic de multo extense numeros de personas reportante al tempore de lor application que illes habeva un consanguineo immediate con diabete, revelava un mortalitate normal pro omne causas de morte in combination. Il habeva in iste gruppo un certe augmento de mortalitate ab diabete e etiam, inter individuos infra 40 annos de etate, un augmentate mortalitate ab morbos cardiovascular-renal. Previe studios del casos de applicantes con al minus duo consanguineos diabetic revelava un moderate augmento del mortalitate in comparation con le norma pro omne causas de morte in combination.

Le resultatos del studio de glycosuria in personas assecurate in le curso de un longe periodo de tempore indica como regula general que individuos con glycosuria "accidental"—i.e. un glycosuria de occurrentia sporadic in certe specimens—ha un prognose favorabile, e mesmo inter individuos con glycosuria persistente que non es clarmente diabetic, il non ha un grave reduction del

longevitate. Le proportion del casos que progrede verso diabete non pare esser grande, secundo lo que es indicate per le mortalitate total o per le mortalitate ab diabete. Il es probabile que le mortes ab diabete in iste gruppo include un certe numero de individuos qui habeva diabete al tempore de lor application sed in qui ille condition non esseva detegite per le examine medical preassecurantial.

In general, individuos non personalmente diabetic sed possedente un consanguineo immediate con diabete non monstrava un diminution significative de lor longevitate ben que le frequentia del subsequente disveloppamento de diabete es supra le norma inter illes.

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The Effects of Vegetarianism

Vegetarians are usually classified as (1) lacto-ovo-vegetarians, or (2) "pure" vegetarians (vegans). Lacto-ovo-vegetarians shun animal flesh (meat, poultry and fish), but eat such foods as milk and eggs, or products made from or containing these. "Pure" vegetarians (vegans) exclude from their diets all foods of animal origin.

M. G. Hardinge and F. J. Stare [*J. Clin. Nutrition* 2:73, 83 (1954)] reported nutritional, physical and laboratory studies on 112 vegetarian (86 lacto-ovo-vegetarians and 26 vegans) and 88 nonvegetarian adults, adolescents and pregnant women. With the exception of the adolescent vegan, the average dietary intake of all groups "approximated or exceeded" the National Research Council recommended allowances. There were no significant differences in the heights, weights and blood pressures of these groups, but the vegan averaged 20 pounds less than the others. Total protein, albumin and globulin values did not differ statistically in the groups, and hematologic studies were similarly negative. As regards pregnancy, the lacto-ovo-vegetarian diet appeared to provide adequate nutrition.

These observations suggest that vegetarianism is essentially harmless, but some recent studies by F. Wokes, J. Badenoch, and H. M. Sinclair [*Voeding* *16*:590 (1955)] indicate that definite illnesses may appear in some vegans of long standing. The group of vegans studied by these British workers consisted of 32 children (13 male, 19 female) of ages up to 18 years, and 117 adults (54 male, 63 female). The commonest and earliest symptoms were in the mouth, particularly sore tongue, but these usually disappeared after a month or two. Paresthesia, amenorrhea and menstrual disturbances, and nonspecific subjective "nervous symptoms" were also noted. Some 20 per cent of the subjects complained of pains in the back and spine, and some had such characteristic stiff "poker" backs that Wokes *et al.* use the term "vegan back" to describe it. These workers emphasize that even slight symptoms did not become manifest until the individual had been on the vegan diet for several years, that more serious symptoms took still longer to develop, and that "quite a number" were apparently symptomless even after more than five years on the diet.

From "Vitamin B_{12} Deficiency in Vegetarians" in *Nutrition Reviews* *14*:73-74, March 1956.

Diabetes for the Diabetics

Ninth Banting Memorial Lecture of the British Diabetic Association

Elliott P. Joslin, M.D., Boston*

Mr. President, Members of the International Diabetes Federation:

How grateful I am for the privilege of being here today and meeting so many friends again from so many countries in the world. And I know that it is because of your friendship that I was chosen to be this year's Banting Lecturer. Of course, I was pleased with the invitation, but became appalled when I looked over the papers of preceding speakers, because they were filled with discoveries and I only have a narrative. However, I am making a little contribution because, annexed to my paper, I am listing all the Banting Lecturers of the past, the topics they discussed and the references to the same. Also, to shorten my talk, I shall have no conclusions, but simply refer to those so well expressed and so consonant with my own ideas in the Banting Lecture of four years ago by Dr. Tunbridge of Leeds. I hope he is present to receive your thanks and mine.

One of my prized possessions is a leaf from the original laboratory notebook of Banting and Best, dated Aug. 6-7, 1921, when they first used the word "isletin." (*Editor: See page 139.*) Their preparation for the test of isletin on the depancreatized dog, proved 100 per cent diabetic by a glucose:nitrogen ratio of 2.8:1, began in the afternoon at 5 o'clock. The first dose of isletin in an 8 cc. suspension was given at midnight when the blood sugar was 430 mg.; by 1 a.m. the blood sugar was 370 mg. and the isletin was repeated; by 2 a.m. 330 mg. and isletin again injected; by 3 a.m. 290 mg. and the fourth dose administered. At 4 a.m. the experiment ended and the blood sugar had fallen to 210 mg.

Will you not rise out of respect and admiration for these two young researchers? They dared to attempt the hitherto impossible, and set an example for youth for all time, Charles H. Best proving *ipso facto* that a medical student should rank as an investigator. Now in behalf of all I say—"Thank God."

When a year later I learned I was to receive insulin, I remember that like Banting and Best I also stayed awake all night. For 25 years I had treated diabetics without insulin and my life was dedicated to the treatment of diabetics.

Here is a letter from Dr. Banting written in 1931, three years before he was knighted, in which he shunned a luncheon in Philadelphia in his honor. This illustrates so well his devotion to his work although ten years had passed since his experiments with insulin. I quote it verbatim.

May 26, 1931

Dr. Elliott P. Joslin
81 Bay State Road
Boston, Massachusetts
Dear Dr. Joslin:

It will be impossible for me to be present. You know yourself that it is silly to leave work in the laboratory for the purpose of attending a luncheon where one's only value is in satisfying the curiosity of the onlooker. I have not the time nor the inclination to prepare a suitable speech, and therefore the only function of my presence is to satisfy the morbid curiosity of the crowd. I have been taken away from my work so much recently that it is piled up and I am determined that I will not leave the laboratory for some months to come.

I hope that you will understand and that you will forgive my seeming ingratitude.

Sincerely yours,
F. G. Banting, M.D.

Upon entering the Harvard Medical School in 1891, my interest in diabetes was so strong, both because of the chemical problems connected with it and because of the year I had spent with R. H. Chittenden at Yale, that I painfully translated the epoch-making paper of Minkowski and von Mering describing their removal of the pancreas. (Imagine how pleased I am now to have the

Presented at the Second Congress of the International Diabetes Federation in Cambridge, England, July 4, 1955.

*Honorary President of the American Diabetes Association, and Honorary President with Charles H. Best, M.D., of the International Diabetes Federation.

daughter-in-law of one of them as a patient.) In the next few years, I failed to profit by their work, despite a hint from a doctor in nearby Groton who told my visiting physician, R. H. Fitz of appendicitis fame, that the condition of one of his diabetics seemed to improve when he ate raw pancreas. How true are Pasteur's words: "In making observations, chance helps the mind that is prepared." But my interest in the disease was so much aroused that my clinical case report before my class in the Medical School was on Mary Higgins, a diabetic, and my Boylston thesis was on diabetes. My being enamoured with the disease became so well-known that my classmate, Harvey Cushing—always up to jokes—in an after-dinner speech presented me with a bouquet of sweet peas!

During twelve months spent in Germany (1896-1897) I do not recall having seen a single diabetic in the clinics of Nothnagle, Neusser and Monti in Vienna or in those of von Leyden, Gerhardt, Senator and Heubneur in Berlin or in Ewald's service under Kuttner in the Kaiserin Augusta Hospital. How fortunate this was. For if one is to treat diabetics he should have the broadest training in clinical medicine, because diabetes is all-inclusive. Is there any other disease which lasts from infancy to old age with complications which involve so many branches of medicine and surgery?

Returning from Europe, I began practice in Boston, with week ends and vacations in that lovely old town of Oxford, Massachusetts, where I was born. On its broad mile-long, elm-lined Main Street stood three adjoining houses as commodious and attractive as any in the village. In them lived three diabetics and I saw them one by one hopelessly suffer and wither away. In fact, of the four couples eventually living in those three houses all developed it, save my father who exercised much and was not overweight. Yet no one thought of a diabetic epidemic, because so many years intervened between the first and last case.

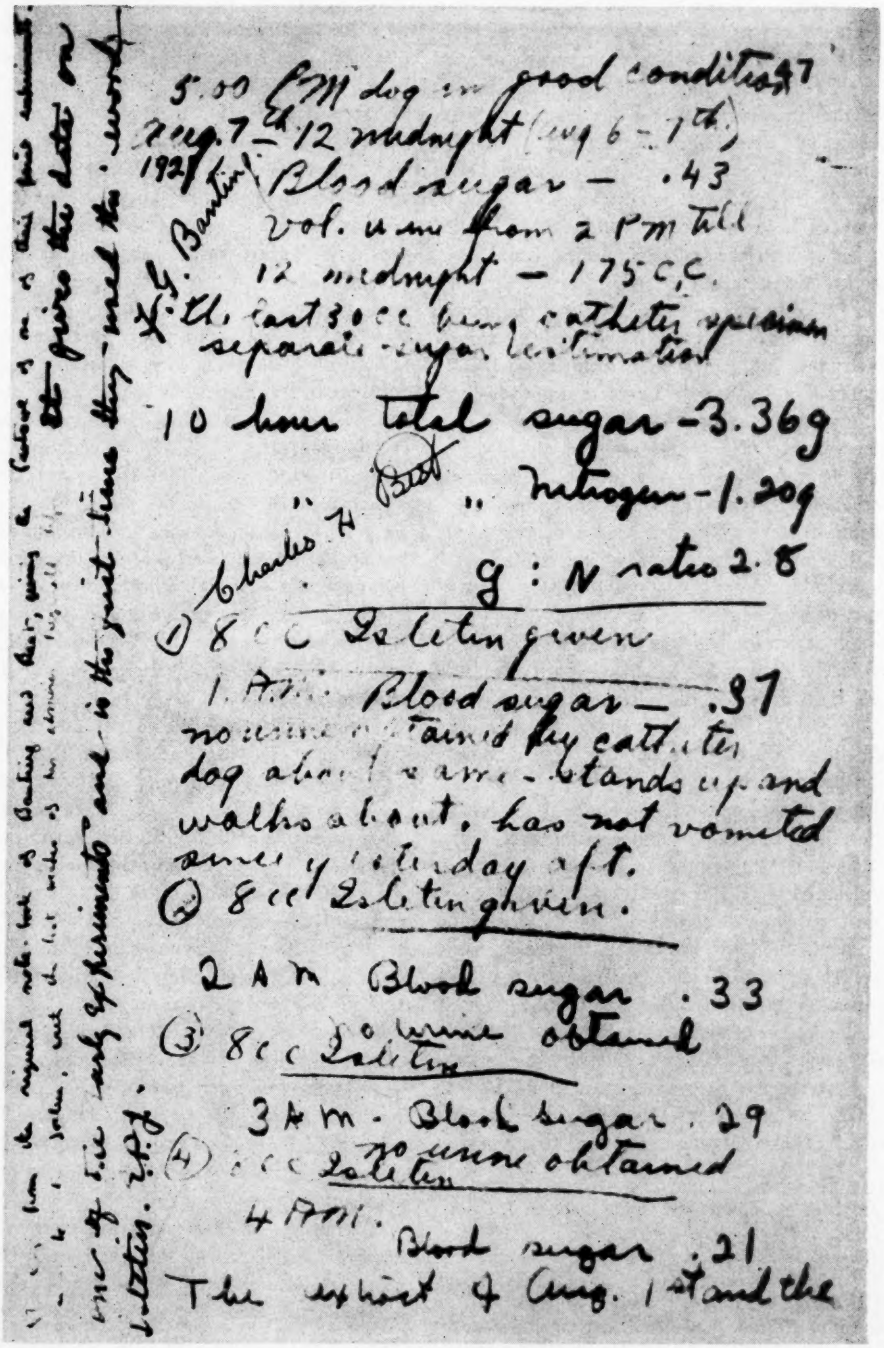
It was then that I examined the records of the Massachusetts General Hospital from its founding in 1824 to 1898 and studied each individual admission to learn those with diabetes. The result of this research was published with the following conclusion: "The practical outcome of this examination of the records of cases of diabetes treated at the Massachusetts General Hospital during the past seventy-four years can be stated in a very few words. The average mortality of saccharin diabetes has not changed materially, for it was the same in the past 13 years as in the previous 61 years. The dietetic restrictions have undergone no essential alteration in this time. Opium is the only drug which has been persistently used in the treatment throughout this entire period."

Such was the background of my knowledge of diabetes when another case developed in those Oxford houses and I recognized its presence in my mother. For her, quite naturally, I sought the best advice in the world and so came under the spell of Naunyn and the Strassburg School. I heard him tell the story of the discovery of the cause of diabetes. There I met Minkowski, Magnus-Levy and Decius Gerhardt whose premature death ended a most promising career. As I now look back upon those early years, I wish that also I might have seen Bouchardat or known his book. If it had been translated into English, German and Italian, it would have saved decades of indifferent treatment. Two weeks ago, it was a consolation to lay a few flowers on his tomb in the Père Lachaise. His hopeful spirit, his adaptation of the crude dietetic teaching of Rollo to a practical daily diet for the patient, his utilization of exercise, his teaching patients to examine their urine and placing on the individual the responsibility for, and the necessity of, the control of the disease, would have helped so much. Subsequently, Petrèn's publications and my personal contact with him helped. All these men were strictly scientific teachers, but also vitally interested in their patients. Magnus-Levy's mother had diabetes and so did Charley Best's aunt and it was the death of the young girl classmate of Banting which turned his thoughts toward this disorder.

As a result of what I learned in Strassburg, my mother lived as long with her diabetes as she was expected to have lived without it. She was the first of the now over 2,000 patients to earn a medal for "Exceeding her Life Expectancy." She never broke the Naunyn diet, never mentioned the disease, resented sympathy, lived bravely, carried on a whole social service of her own for the old, the decrepit, rescuing alcoholics in my father's factory, but delighting most of all in her children's sewing and Sunday School classes. She was the epitome of "Diabetes for the Diabetics."

Von Noorden's early writings and his popularization of the metabolism of diabetes and its management were a great asset, and the conundrum of the oatmeal treatment and its fallacy were really advantageous. We learn almost more by our mistakes. Hodgson, a country doctor in Waukesha, Wisconsin, taught me one fundamental principle—not to overfeed my patients—and one of my teachers, who knew little about diabetes, was so good a practitioner that he laid down another rule, namely, never suddenly change the habits of any diabetic of long duration.

My respect for diabetics developed in those gruelling days when Frederick M. Allen introduced the fasting treatment and demonstrated that diabetes could be controlled, though often at a sacrifice of nutrition. Allen



5.00 P.M. dog in good condition
Aug. 7 — 12 midnight (Aug 6 — 7th.)
1922 F. G. Banting Blood sugar — .43
Vol. urine from 2 P.M. till
12 midnight — 175 c.c.
The last 30 c.c. being catheter specimen
separate sugar determination
10 hour total sugar — 3.36g
" Nitrogen — 1.20g
G : N ratio 2.8
(1) 8 c.c. Insulin given
1 A.M. Blood sugar — .37
no urine obtained by catheter
dog about 2 A.M. stands up and
walks about, has not vomited
since yesterday a.m.
(2) 8 c.c. Insulin given.
2 A.M. Blood sugar .33
(3) 8 c.c. Insulin No urine obtained
3 A.M. Blood sugar .29
(4) 8 c.c. Insulin No urine obtained
4 A.M. Blood sugar .21
The exhibit of Aug. 1st and the

was encouraged by Naunyn's and von Noorden's previous use of fasting days, as well as by Guelpa's crude methods. Then it was that one learned the metal of his patients and their trust and confidence in their doctor. There was a thrill in the knowledge that undernutrition had changed the prognosis and that the length of life of the fatal cases had been 6 years instead of 4.9 years—a gain of 20 per cent—and that deaths from coma had dropped from 63 to 41 per cent.

No student of diabetes today should fail to read Allen's articles* which showed what fasting could accomplish in diabetic beast and diabetic man.

Petrèn and I tried to make diabetes as safe in the home as in the hospital. Case after case fought starvation for years. The struggle in them and in their medical advisors engendered a Cyrano de Bergerac attitude—the joy of fighting even if you knew you must lose. I remember how von Noorden turned away in disapproval when he saw Ruth A. in 1921—17 years old, height 5 feet 3/4 inches, weight 54 pounds. She was hardly more than a skeleton. Yet von Noorden died a quarter of a century ago, but my Ruth is alive today and active in an orthopedic doctor's office in Chicago thirty-four years after the onset of her diabetes.

The character which the belief in the principle of fasting created in the patient led me to a regard for diabetics which time does not dim. The earnest patients then felt that each honest diabetic day they lived not only helped themselves but helped every other diabetic, and they acquired a missionary zeal.

On March 30, 1920, there came to my office a woman with diabetes. She was given the usual examination with suggestions for treatment, and as it was impracticable for her to enter the hospital, she was taught on the spot to examine her urine. She went home and shortly after contracted pneumonia and died. But in the intervening days amid her household cares she took enough interest to examine the urines of ten others in her boarding house, and discovered the presence of diabetes in a boy. She sent him to his own physician, and eventually the boy came to me, telling this story. At the time she learned the Benedict test and made these urinary examinations of her friends, Louisa Drumm was seventy-nine years and four months old.

To make plain why I think diabetes is for the diabetic, may I summarize the present situation as I see it from my contact with those for whom I have cared since 1897? I acknowledge I have treated many diabetics, but when I compare Rollo's 7 cases and Naunyn's 777 cases with my gross numbers, I feel embarrassed and especially so when I realize I have never cured one diabetic patient and 15,795 of those I have treated have died. However, with my emphasis on the control of even the merest sign of diabetes and its aggressive handling, I cannot help the thought that some patients had their latent Marañon period of diabetes so much prolonged that frank diabetes never showed itself. Please bear with my statistics because only by comparing past with present results in the treatment of a chronic disease can any doctor have the fortitude to try again when the next new case appears.

Between 1897 and 1914 the average duration of life of the fatal cases was 4.9 years and between 1950 and 1955 it was 16 years. In the early period, the average age at death of the patients was 45 years and it is now 64 years. With this notable gain in longevity I am not content, because it is actually less than that of the total population in the same number of years. At first, two-thirds, or 66.8 per cent, died in less than their first 5 years of the disease, but now one-tenth or 10.6 per cent do so. Up to 1914, 1.8 per cent of the fatal cases reached a duration of 20 years or more but now 32.7 per cent do. We have seen 4,048 diabetic children with onset under 15 years of age. Of these we traced, in 1954, all but 23 and found 3,032 were alive and 993 dead. Among children whose onset of diabetes was in the first decade of life in the Naunyn era, the fatal cases lived for 1.3 years, but now the duration of life of such cases is 20.8 years. We know that 1,072 of our diabetic children have lived over 20 years with diabetes. Thanks to a gift of an anonymous gentleman, who happens to be in this audience, a most detailed analysis of these patients is being carried out.

Kindred to this group are Dr. Priscilla White's obstetrical patients. These number some 1,200 over the last 19 years and certainly present a pressing problem, and their offspring still more so. Dr. White tells me that of 813 of the more recent viable cases, i.e., 28 weeks gestation, 661 were treated with hormones with 89 per cent survival.

The causes of death of diabetics have also changed markedly. Coma, tuberculosis and, most cheerful of all, gangrene have fallen to almost exactly 1 per cent, indicating we are even beginning to cope with arteriosclerosis.

A word about cancer. It now causes 10 per cent of the deaths. We are in the midst of a survey of the incidence

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TABLE 1

Average duration of life subsequent to onset of diabetes among 15,795 deceased ex-patients in each of the important eras of treatment. By age group at onset.
(Experience of Joslin Clinic, 1897-1955)

Age groups at onset	Naunyn Era 1897 to 5/31/14		Allen Era 6/1/14 to 8/6/22		Banting Era 8/7/22 to 12/31/29		Banting Era 1/1/30 to 12/31/36		Hagedorn Era 1/1/37 to 12/31/43		Chas. H. Best Era 1/1/44 to 12/31/49		Chas. H. Best Era 1/1/50 to 5/3/55	
	No. of cases	Duration yrs.	No. of cases	Duration yrs.	No. of cases	Duration yrs.	No. of cases	Duration yrs.	No. of cases	Duration yrs.	No. of cases	Duration yrs.	No. of cases	Duration yrs.
All ages	326	4.9*	836	6.1*	1,457	8.0*	2,695	10.3*	3,615	12.1*	3,969	13.8*	2,897	16.0*
0-9	24	1.3	61	2.9	21	2.8	24	7.3	36	10.3	58	18.5	81	20.8
10-19	39	2.7	84	2.7	56	3.4	60	7.4	79	11.4	125	16.2	163	20.3
20-39	85	4.3	215	4.9	198	8.9	275	14.4	398	16.9	454	18.9	448	22.2
40-59	126	7.0	351	8.0	800	9.5	1,457	11.6	1,906	13.4	2,127	15.0	1,465	16.4
60 & over	51	4.4	117	6.4	379	5.5	859	7.0	1,195	8.6	1,192	9.2	736	9.9
Unknown	1	—	8	—	3	—	20	—	1	—	13	—	4	—

*Based on cases with known duration.
Note: Deaths reported through May 3, 1955.
The compilation of this table was made by the Statistical Department of the Metropolitan Life Insurance Company with help from the Nordisk Insulinfond, Diabetes Foundation, Inc., and the Joslin Clinic and thousands of patients, doctors and Boards of Health.

TABLE 2

Duration of life subsequent to onset of diabetes among 15,795 deceased ex-patients in each of the important eras of treatment. Number and per cent of cases classified according to duration.
(Experience of Joslin Clinic, 1897-1955)

Duration years	Naunyn Era 1897 to 5/31/14		Allen Era 6/1/14 to 8/6/22		Banting Era 8/7/22 to 12/31/29		Banting Era 1/1/30 to 12/31/36		Hagedorn Era 1/1/37 to 12/31/43		Chas. H. Best Era 1/1/44 to 12/31/49		Chas. H. Best Era 1/1/50 to 5/3/55	
	No. of cases	Per cent	No. of cases	Per cent	No. of cases	Per cent	No. of cases	Per cent	No. of cases	Per cent	No. of cases	Per cent	No. of cases	Per cent
All cases	326	100.0	836	100.0	1,457	100.0	2,695	100.0	3,615	100.0	3,969	100.0	2,897	100.0
Less than 5	217	66.8	463	55.9	592	40.7	643	24.0	607	16.8	531	13.4	307	10.6
Less than 1	63	19.4	72	8.7	74	5.1	110	4.1	77	2.1	67	1.7	53	1.8
1	51	15.7	108	13.0	131	9.0	111	4.1	105	2.9	102	2.6	57	2.0
2	53	16.3	121	14.6	125	8.6	116	4.3	118	3.3	104	2.6	52	1.8
3	23	7.1	97	11.7	128	8.8	158	5.9	157	4.3	125	3.2	72	2.5
4	27	8.3	65	7.9	134	9.2	148	5.5	150	4.2	133	3.4	73	2.5
5–9	58	17.8	210	25.4	401	27.6	822	30.7	879	24.3	886	22.4	473	16.3
5	18	5.5	49	5.9	99	6.8	157	5.9	169	4.7	150	3.8	81	2.8
6	10	3.1	51	6.2	86	5.9	167	6.2	167	4.6	179	4.5	91	3.1
7	9	2.8	46	5.6	86	5.9	172	6.4	195	5.4	185	4.7	90	3.1
8	16	4.9	36	4.3	71	4.9	160	6.0	169	4.7	192	4.9	95	3.3
9	5	1.5	28	3.4	59	4.1	166	6.2	179	5.0	180	4.6	116	4.0
10–14	32	9.8	89	10.7	246	16.9	620	23.2	993	27.5	898	22.7	624	21.6
15–19	12	3.7	40	4.8	145	10.0	349	13.0	678	18.8	825	20.9	543	18.8
20 or more	6	1.8	26	3.1	70	4.8	241	9.0	457	12.6	816	20.6	946	32.7
Unknown	1	—	8	—	3	—	20	—	1	—	13	—	4	—
Average*	4.9		6.1		8.0		10.3		12.1		13.8		16.0	
Median*	2.9		4.3		6.4		9.2		11.5		13.1		15.4	
Average age at death	44.5		46.7		57.9		63.0		65.0		65.3		64.3	

*Based on cases with known duration.
Note: Deaths reported through May 3, 1955.
The compilation of this table was made by the Statistical Department of the Metropolitan Life Insurance Company with help from the Nordisk Insulinfond, Diabetes Foundation, Inc., and the Joslin Clinic and thousands of patients, doctors and Boards of Health.

TABLE 3

Causes of death in 600 patients with onset of diabetes under the age of 15 years*

Period	1898 1922	1922 1936	1937 1943	1944 1949	1950 1953
Number of patients dying	157	99	81	144	119
Cause of death (%)					
Diabetic coma	86.0	56.0	27.2	9.7	6.7
Coronary heart disease	–	–	2.5	10.4	5.9
Nephropathy	–	2.0	12.3	36.8	63.0
Cerebro-vascular accident	–	–	1.2	2.1	5.9
Infections†	6.4	23.2	24.7	6.9	8.4
Tuberculosis	–	8.1	9.9	11.1	1.7
Other	7.6	10.7	22.2	23.0	8.4

*Compiled by Statistical Department, Metropolitan Life Insurance Company, from experience of Joslin Clinic. Adapted from table prepared by author and published in *Maryland State Med. J.* 3:8-13 (Jan.) 1954.
†Excluding tuberculosis.

of cancer in diabetes as compared with that in the general population and later will report upon it.

As for the causes of death for all ages, cardio-renal-vascular disease accounts for 76 per cent of the total deaths of 656 patients preceding April 17, 1952. This figure is made up of cardiac deaths, 47.6 per cent, cerebral and renal each 13 per cent, with gangrene 1.1 per cent. Infections constitute 5.8 per cent and a miscellaneous group of cases make up the remaining causes of which only 0.2 per cent was assigned to an insulin reaction.

I am quite sure that since 1952 these figures have changed materially. The most recent data for fatalities at my disposal are those of my colleague, Dr. Alexander Marble, which relate to 600 patients with onset of diabetes under the age of 15 years. These 600 represent the total deaths of the diabetics in childhood seen between 1897 and 1953.

Before 1922, coma accounted for 86 per cent of the mortality of these children but since 1950, 6.7 per cent. Nephropathy was represented by no deaths in the earliest period but in the most recent, 63 per cent. This shows the rapid change which has occurred in the causes of death of diabetics. Infections, which were once responsible for 24.7 per cent of the deaths, now are 8.4 per cent and tuberculosis, instead of 11.1 per cent, now is 1.7 per cent. In this connection I would mention that my colleague, Dr. Howard F. Root, has collected over 500 cases of retinitis proliferans, a condition which earlier was seldom seen. From the Department of the Blind in Massachusetts for the year 1950, of the new cases of registered blindness there were 8 per cent due to diabetes, but for this year, 1955, the figure has risen to 18 per cent, because so many diabetics are living longer to lose their eyesight. It is true that diabetics do not die of complications in the eyes, but such complications are so serious and so often associated with conditions which shortly lead to a fatal outcome that they merit special attention. At your Frederick Banting Home I noted 1 of the 29 patients was blind, 4 nearly blind and 6 others were at least partially blind.

Such then is the statistical background as we consider the status of present and future diabetics; to summarize it, the diabetics are living three times as long, are dying twenty-years older than formerly, and then 85 per cent die of distressing complications which usually last for years, and yet we are sure these are avoidable.

The recognition of the problem has been advanced by the appointment of our colleague, Dr. Raoul Boulin, as Professor of Diabetes in the University of Paris, the first such Professorship in the world. In his inaugural address, he called attention to the magnitude of diabetes when he estimated there are 20,000,000 diabetics in the world. Diabetics form a significant segment of society. We know many of them are notable like my patient, George Minot, who with his associates Murphy and Whipple, received a Nobel Prize for the discovery of the effective treatment of pernicious anemia with liver extract; or those two Marshals of France and Clemenceau who as diabetics in the First World War obtained distinction by their outstanding success. Here in England you are well aware of diabetics who have been leaders of public opinion, and you know full well whom I regard as the world's outstanding living diabetic, our President, Dr. Robin D. Lawrence. I believe this International Meeting should encourage diabetics to organize to make known as a group their numbers, their capabilities and the pos-

sibilities they can exert for promoting the best for themselves, the community and for medicine. That is why we need this world-wide organization. Anything we can do to increase its spread and influence anywhere will increase the good it accomplishes everywhere.

We should also do more to raise the standards for treatment of diabetics. I recommend the extension of the policy of awarding Medals to those diabetics who by their lives have accomplished far more than the average. I believe the knowledge that Mrs. Dow celebrated her 100th birthday June 9, and that she wore our Gold Medal for having lived more than twice as long with her diabetes than she was expected to live without it, should rank in importance with an *arbeit* from a laboratory. The appearance of such individuals before a class of diabetics is convincing proof that diabetes is controllable and does far more good than hours of teaching. For our Quarter Century Victory Medal we had only one candidate in 1948, but now there are 59 who have received it because of a sound body and perfect eyes and blood vessels.

There must be many more of these Quarter Century Victory Medal Cases in many lands and these cases should be sought out, shown in medical meetings and honored and the reasons given why they have done so well. We believe it will be learned that they are the ones who have controlled their disease most meticulously.

The idea has been raised that a diabetic should not feel he has done wrong if he has a poor Benedict test. I disagree. When I see a red test, I know, if uncorrected, that patient is headed for destruction. I believe he should be happy when he knows his faithful following of the rules ends with a blue victory. Oliver Wendell Holmes said in his paper on the prevention of childbed fever, "I am too much in earnest for either humility or vanity." I feel the same. It has been customary throughout the world and at all times to reward unusual conduct. We give awards in schools. Each year we give degrees at our universities. Outstanding achievements in any line receive attention. Why should not a diabetic who lives an honest diabetic life be afforded recognition? Diabetes is a disease in which each patient and each doctor can and should be a pioneer and thus contribute to the good of the whole group.

Diabetes is for the diabetics, but the disease carries with it heavy responsibilities. All agree diabetes is hereditary. Two diabetics should not marry one another and have children under present conditions. Diabetics should choose for partners those in whose families the disease is absent or rare. Responsibility for the transmission of diabetes is squarely up to the diabetic. Furthermore, we know the development of the disease in the vast majority of the cases is in those who are overweight and therefore it rests upon the diabetic to see to it that not only he but none of his relatives are allowed to be fat. Even in young members of a diabetic family, we doctors should strive by moderate restriction of the diet not to allow the children to grow tall prematurely. We should anticipate the development of diabetes as Marañon began to teach us years and years ago, and I understand Professor Boulin will advocate it in a paper in the near future. From a different point of view, Professor Hoet has preached it for the last few years.

The early recognition and detection of diabetes also rest upon the diabetic, because he knows that it is more apt to occur in the families of diabetics and, therefore, should routinely test yearly all his relatives. Who is more interested than he to discover an unsuspected case?

Diabetics have a heavy responsibility according to the occupations they pursue. Consider the driving of automobiles. For years I have urged diabetics never to go over two hours when driving without carbohydrate, but last month I went a step further and asked the representative of our Registry of Motor Vehicles to address a class of diabetics at its morning session. I told him he could talk for five minutes but actually the diabetics plied him with so many questions that he was not allowed to sit down for thirty minutes and the give and take between the diabetics and the representative of the Registry of Motor Vehicles was most enlightening. Such problems should be met squarely and openly. He told them that if they applied for a license and did not state in their application that they had diabetes, they were liable to a fine of $200 for perjury and that if they had an accident under such circumstances, it was quite possible that the insurance company would refuse liability. But conversely it was brought out that he did not know how many diabetics there were among those already granted licenses and he did not know how frequent it was for diabetics to have accidents as compared with nondiabetics. When I told him my patients were exceptional individuals and taught to be very careful indeed, and that it might well prove to be that they were among his safest drivers, there was applause. It may well be true. This shows why I think diabetics should organize and be united and work out the solution of such problems.

Similarly in dealing with insurance companies there is need for organization. True it is that rates will not be lowered until each diabetic does his best and lives longer. What I want is for an insurance company to tell my diabetics, when they take out insurance, it is true that we charge you an extra premium but if you will live beyond the standard number of years then the cost of your premiums will be reduced and if you live ten years more, then you need pay no more premiums at all!! Why

should not insurance companies give our diabetics an incentive to live long? Consider my own situation and what a stimulus it has been to me to keep alive. The Nordisk Insulinfond some years ago gave $50,000 to the American Diabetes Association with the understanding that I was to expend the interest as long as I lived. What a splendid time I have expending that income and using it to demonstrate by statistical summaries that diabetics can live longer than they were expected to live. That would have pleased Bouchardat.

If a diabetic has a job, it is up to that diabetic to show that he can fill that job better than a nondiabetic. A thousand positions are open in our Civil Service for diabetics. Mrs. S. tells me in four years at the bank not only has she not missed a day for illness, but that she is the only one of the employees with such a record. What an incalculable asset she has proved to be for other diabetics in her community. Another diabetic has worked for the General Electric Company and in thirty years has not lost more than one day yearly. Now he has 200 employees under him. At one time last year we had fourteen diabetics earning salaries in our own various undertakings.

Diabetes is for the diabetics and it is also for the diabetic to provide funds for research. No one else is as interested as the diabetic because it was by research on a dog that his life was saved by the resulting insulin. Vivisection under suitable control must be supported and diabetics are the ones to make it understood that it is necessary. In the last 10 years we have had at least 10,000 separate contributions to our diabetic funds.

I would rather have a dollar from each one of 1,000 diabetics than $1,000 from one. Whenever a diabetic gives $1.00 for research, it means he is interested in his disease and will take better care of himself. Moreover, the $1,000 donor may die, but many of the dollar donors are likely to live and give again. There are upwards of two million diabetics in the United States. If each one of them saved one cent a day, the equivalent of one cigarette, not counting Sundays, we would have $6,000,000 for their own protection. There are plenty of diabetics in the United States; plenty of them have ability to work and they resent being thought incapable. Diabetics are cheerful givers, but their gifts place a tremendous responsibility on those of us whom they trust to administer them. To each stockholder in our Diabetes Foundation we must provide an account of our stewardship. I do not think the story of Banting and Best is told often enough. At one stage in their work, Banting sold his automobile to keep on with his experiments.

I hope diabetics will not ask for public support as is the case in our country with societies for tuberculosis, for cancer, for polio, for multiple sclerosis, arthritis and for heart disease. Diabetics can pay their own way and take care of research and to a large degree for the care of the complicated case. If they do so, think of the respect they will create for themselves in the community. The American Diabetes Association recently voted not to appeal to the public for funds and I understand this is the policy of The Canadian Diabetic Association.

Responsibility for his disease is essential if a diabetic is to have a successful career. It is extraordinarily difficult to treat diabetics in an outpatient clinic where their payment for care is zero, because then they do not feel their responsibility. Even if they pay but a pittance, adherence to treatment is greater than as if they contribute nothing. It will be extremely interesting to watch the results here in England where medical care is provided, compared with countries where a certain proportion of the people pay something toward it.

However, remember one can learn much by visiting countries where diabetes is treated in different ways from those to which one is accustomed. Years ago I found that when I visited a hospital where treatment seemed bizarre, if I would stay long enough to study the whole situation I would find that there was a good reason for the peculiar methods employed. What applies to clinics applies to nations. Learn from each but do not tell another country how to treat its diabetics. In each country conditions are different and treatment must be suited to its peculiar needs.

Fresh statistics about the incidence and duration of life of diabetics in various countries of the world are required. The published statistics about the incidence of diabetes and the causes of death are most inaccurate and so it depends upon individual doctors or groups of doctors to furnish data which are reliable. I personally check each diabetic death. If it is put down "coma" and I do not know the circumstances, I write the doctor or the hospital to find out whether it was diabetic, uremic or cerebral coma. In any case in which the word "diabetes" is put down as the cause of death, I write the doctor who signed the death certificate asking him if there were not some complications. In our published causes of death, diabetes as a cause of death seldom exceeds one per cent. Frequently we check our positively known duration of the disease with the duration as specified by the doctor who signed the death certificate and the difference is often enormous, showing the inaccuracy of such statements in public records where the doctor who signs the certificate does not know the full life history. I think it is probably correct to say that the average diabetic outlives his original doctor.

Diabetic Camps: Last year we had 384 children at our

diabetic camps. The cost was about $7.00 a child a day. We send out letters to all our children who are eligible and frankly state that no child should stay away for inability to pay the whole or even a part of the camp fee. There have been few instances in which there was abuse of our offer for free care. As a matter of fact, the cost of the camps was $69,000 and the children paid $34,000. Families of diabetics love to give money for children in diabetic camps. Give them a chance to do it.

Diabetic camps are splendid and the increasing number of them throughout the world proves their usefulness. I estimate there are at least twenty-six in the United States. We need more, because the diabetic children should have diversion and supervision under pleasant circumstances. "All work and no play makes Jack a dull boy." The camps likewise give relaxation to the families of diabetic children and those caring for diabetic children require a vacation, almost as much as the children themselves. But now we are way beyond the camp stage. Children do not die in camps; the next fifteen years is their critical period. Do you know what happens to your children after they have had diabetes fifteen years? Today for the younger diabetic and those of short duration, teaching takes precedence over nursing and is less expensive, because it can be done partly in classes. With advancing age and duration of the disease, nursing takes precedence over teaching, because complications require so much attention. Patients must be taught so that 85 per cent of them can escape complications in the eyes, kidneys, and blood vessels after 15 years. It is teaching, not nursing, which is essential to bring this about. Evidence enough has accumulated so that we know, if the rules of the game are followed, particularly in the early years of the disease, there can be healthy eyes, arteries and kidneys even after an interval of twenty-five years. Our fifty-nine Quarter Century Victory Medal cases have demonstrated this. They are in general those who in early life had the opportunity to learn about and follow careful treatment.

The Hospital Teaching Clinic: We are building it so that all our hopeful cases will be given an opportunity to have help. It is the Hospital Teaching Clinic which I believe will foster such cases and thus give a new hope. The Hospital Teaching Clinic is a place where ambulatory diabetics can return for instruction and encouragement at low cost.

If you have a Hospital Teaching Clinic, treat those who come as students. Don't treat these healthy diabetics as sick diabetics. Of course they will want to enter in the late afternoon, when they have completed their day's work, will want to come week ends and holidays, will want early breakfasts and late evening meals as they do at home and be treated so energetically that they need remain but a few days. What the patients wish is the opportunity to see how they can and should live and to discover their mistakes. In this Hospital Teaching Clinic laboratory tests must be done for cost and not to support those other activities in the hospital which are a drag on the institution. In the Hospital Teaching Clinic wholesale methods should also apply to X-ray examinations and electrocardiograms. Great care should be exercised that only directly useful tests are employed and not for curiosity and research. Such tests are most desirable under certain circumstances, but in this Hospital Teaching Clinic costs must be minimal. Such patients can do light housekeeping as boys and girls do in boarding schools. I consider the Hospital Teaching Clinic idea—the idea that each hospital in the world should have at least a few inexpensive beds for the early and hopeful cases of diabetes where diabetics can learn how to maintain their health at little cost—the most important addition to the care of diabetics which is possible of general and immediate adoption. It will not be easy to lower hospital costs and to reduce costs paid for routine examinations of urine and blood, but it can be done.

When this has been accomplished for the ambulatory patients, then the far more expensive, but less dividend-returning problem can be attacked of caring for the patients with circulatory diseases of the lower extremities. Now, such a case, my colleague, Dr. Root, has found, stays in the hospital on an average of twenty-eight days, having been ill at home about as long before entrance; when his stay is finished he is usually discharged handicapped. The cost of caring for one such individual is five to ten times that for caring for a young and hopeful case whose life may be prolonged for years of activity.

Today we have learned how to treat diabetics so well that with our present methods we know our patients should live twice as long as they do because of their greater knowledge of medicine and hygiene. A large proportion should outlive the ordinary life expectancy of those about them.

Who learns and learns
Yet does not what he knows,
Is one who plows and plows
Yet never sows.

It is for you and me to be more aggressive, to be willing to be explorers, to have the courage of a Columbus and write in our log as he did in his—"And this day we sailed on W.S.W."

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Teaching the Diabetic Patient

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Diabetes is a lifelong disease requiring more participation by the patient in his own care than most other diseases. His role is the important one in achieving the best regulation and thus preventing both metabolic and degenerative complications. In addition, normoglycemia can cause a decrease in the symptoms of both dynamic (infection, neuropathy) as well as structural (coronary and peripheral arteriosclerosis) complications. Recent studies[1, 2] have shown the striking importance of self-care in preventing or postponing necrosis and infection of the legs even in diabetic patients with advanced peripheral vascular disease.

While the value of proper patient education has never been questioned, the degree of success achieved currently has been. An opportunity to evaluate the latter was presented by the Boston Diabetes Fair held yearly under the auspices of the New England Diabetes Association. In 1952, the Subcommittee on Patient Education* of the Diabetes Committee of the United Community Services of Boston questioned 128 diabetics (of whom 110 were under private care and 18 from various Greater Boston Diabetes clinics) who visited the Fair† and 110 patients in six Greater Boston hospital diabetes clinics. Ten standard questions were used which gave a representative though not complete survey of the patients' knowledge of diabetes. These were multiple choice questions as follows:

QUESTIONNAIRE ON DIABETES

Check the ONE answer under each question that is the BEST answer.

1. If you have a large amount of sugar in your urine, the urine test would show:
   a. Blue
   b. Orange
   c. Olive
   d. Green
2. What changes should you make in your diet if you have a severe cold?
   a. Omit meals
   b. Add extra orange juice to diet
   c. Take liquid diet that gives same food value
   d. Eat whatever you can

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The major portion of this article is taken from an address given to the Six-Hospital Conference on Methods of Teaching the Diabetes Patient held at the Boston United Community Services' Mason Memorial Building on April 13, 1955. This conference was held for the purpose of coordinating and improving patient diabetes teaching and was sponsored by the Subcommittee on Patient Education (Samuel B. Beaser, M.D., Chairman) of the U.C.S. Diabetes Committee (Howard F. Root, M.D., Chairman).

* Then under the chairmanship of Dr. Henry K. Bakst.

† I am indebted to the members of that committee who collected and analyzed data: Mrs. Elizabeth Caso, and Misses Lena DiCicco, Ann Ryan, Evelyn Rosen, and Ruth Richards.

3. What food can be taken in place of 1 egg?
   a. ½ cup oatmeal
   b. 1 slice cheese
   c. ½ cup baked beans
   d. 1 cup milk
4. How does the diet for the person with diabetes differ from the normal diet?
   a. Contains more vitamins
   b. Omits cereal
   c. Is low in meat
   d. Is regular in amount
5. Which group of foods should be divided among the day's meals?
   a. Liquids
   b. Carbohydrates
   c. Seasonings (salt, pepper)
   d. Vegetables
6. Can a diabetic have children?
   a. Only by adoption
   b. Yes they can
   c. No they cannot
   d. Only if one parent is not a diabetic
7. Which one of the following may cause an insulin reaction?
   a. Infection
   b. Omitting insulin
   c. Strenuous exercise
   d. Overeating
8. Good foot care includes:
   a. Cutting corns regularly
   b. Bathing of feet
   c. Walking barefooted
   d. Using hot water bottle to warm cold feet
9. Insulin dosage is measured by:
   a. Cubic centimeters (cc.)
   b. Drops
   c. Units
   d. Grams
10. The normal blood contains:
    a. Some sugar at all times
    b. No sugar at any time
    c. Sugar only after eating
    d. Sugar in the morning only
11. How often do you test your urine?

The results showed that all were distinctly deficient in knowledge of their disease.

It is the common impression among those dealing extensively with diabetic patients that both new and old patients are equally in need of education and at least yearly re-education. Both groups have their share of misconceptions about the disease. Moreover, it is fallacious to assume that a diabetic, however long his course, has been properly indoctrinated at the onset or subsequently. In addition, the elderly diabetic is extremely forgetful. Thus, in numbers those with old diabetes constitute the largest group to be taught and the greatest challenge.

In the past we have failed to capture the interest and enthusiasm of the diabetic patient for continual and lifelong self-care. There has been an overemphasis on giving the patients purely medical facts, and not enough attention to influencing and promoting proper psychological attitudes toward the disease. Such errors of omission are of different sorts.

The diagnosis and prognosis of diabetes are not explained to a large proportion of patients convincingly enough at the onset of the disease. Diabetes is diagnosed in the majority of patients by casually discovered glycosuria. Many physicians still have difficulty accepting the concept that this asymptomatic stage of diabetes is an early phase of a disease, even though they have been conditioned to do so in other disorders such as leukemia, uremia, cancer, and others. Consequently, the majority of patients too frequently receive a halfhearted diagnosis couched in vague terms of "sugar in the urine or blood"; often even the use of the term diabetes is omitted. Little wonder that these patients entertain doubts regarding the reality or significance of their disease, for their physicians do not offer them adequate teaching.

In some diabetics, after proper therapy has normalized the laboratory findings, the patients may be erroneously told that the diabetes is cured or never existed. The patients only too willingly grasp at this straw and may disappear from medical purview. Subsequently, the disease or its complications is likely to return them to the fold much the worse for the experience.

PRINCIPLES OF PATIENT EDUCATION

All categories of patients will benefit by having the following principles impressed on them firmly:

1. It is important to emphasize the permanency of diabetes if the self-care and dietetic self-denial are also to be permanent. Psychologically, any shock caused by this concept can be cushioned by citing reassuring statistics on the longevity of diabetics.

2. Next, we must sufficiently delineate the changing and dynamic character of diabetes under the influence of other complicating diseases, or even arising spontaneously. This reinforces the need for continual and permanent medical supervision.

3. We should provide the proper knowledge of the potential seriousness of diabetic complications for the same purpose.

4. It is important to recognize how potent psychologically are the appetite urges which diabetics are being asked to restrain. Most diabetics are obese and probably have had an above average appetite so that dieting represents a relatively great sacrifice. In return for these sacrifices, we must offer them some positive psychological satisfactions in terms of better health, economic adjustment, successful childbearing, and so forth. This requires

a personal approach to each patient as an individual in his family or community setting.

5. Finally, physicians should remember that the problems posed by diabetes are very complex for patients, especially for those of advanced age. After a few years of poor regulation, mental and personality changes ensue in diabetics of any age and they become forgetful, stubborn and opinionated. Two difficulties then appear: the discrepancy between the problem and the capability of the patients increases and, due to poor judgment, the division of authority between doctor and patient becomes increasingly hazy in the latter's mind. It is, therefore, important to try to set definite limits to the patient's role in self-treatment in the initial teaching, and this should be re-emphasized from time to time.

The actual content of diabetes teaching material may be relatively clearly defined and can be conveniently subdivided into specific areas. Some of these topics require individual instruction, while some lend themselves to group teaching. For example, the sensitive subject of the description of the disease and its complications is best given by physicians personally and individually to patients to avoid psychological trauma.

Written material is an adjunct and not a substitute for personal teaching with its opportunity for individualization. Yet, there are some definite advantages to the former. The most obvious is permanency. Then, too, there exist some, though not large, differences of opinion with regard to some of the content of diabetes teaching material. There is less confusion for the patient if the views on these controversial areas are committed to writing as in a hospital diabetes manual.

CLINICAL PROBLEMS REQUIRING PATIENT EDUCATION

It may be profitable to point out from practical clinical experience the critical areas in diabetes education in which our program more commonly falls down.

There exists the paradox that only a small fraction of patients are permanently well regulated, even though 80 to 90 per cent could be by the use of the improved types of insulin. This is most often due to the failure of education or to lack of cooperation by the patient with respect to diet, even though the degree of dietary cooperation required for normoglycemia is only a day-to-day constancy of $\pm$ 15 to 20 per cent. Less frequently, it is due to lack of understanding by patients that a correct diet is still the important prerequisite even when insulin is added to the regimen.

In insulin-treated patients, unsatisfactory metabolic regulation is frequently accompanied by insulin reactions. Only a small minority of these reactions are due to actual lability of the diabetes or "brittleness," although they are usually so labeled. Actually both physician and patient can profit by adopting the optimistic point of view that insulin reactions are usually avoidable by scrupulous attention to the details of diet or insulin administration.

It must be made clear to the patient that with the use of continuous and long-acting insulin, regularity of food intake including the bedtime snack is a necessity. The patient, if not properly briefed, may extend the allowable freedom of food-equivalent exchanges within each meal to the license to make unphysiological shifts from meal to meal. Diet prescriptions which include a total 24 hour food list encourage this error.

Reactions are less frequently due to misconceptions regarding insulin administration. On the part of the physician, reactions may be due to the routine prescription of NPH insulin to all diabetics requiring insulin without an awareness that fully 30 per cent require different ratios of long to short acting insulins. On the part of the patient, errors occur from the use of combination U40-U80 syringes or the inadvertent substitution of syringes when purchased without prescription. More avoidable are the errors resulting from the granting of permission to the patient to alter insulin dosage by urine test without explicit and written instructions.

Occasional insulin hypoglycemia is almost unavoidable in some patients regulated to the point of normoglycemia. Yet, this too can be minimized by proper education. The need for extra food can be anticipated for those in whom exercise has a hypoglycemic effect. Further, such patients can be taught to recognize minor degrees of hypoglycemia which frequently occur at set hours for days prior to the apparently sudden occurrence of a severe attack.

Diabetic coma still occurs, although it is becoming rarer. Coma may occur repeatedly in a given individual as a result of a personality disorder. It is important to recognize the psychological rather than the physiological basis for the regulation defect in such patients in order to effect a permanent solution. In patient education, a routine description of diabetic coma is insufficient. Emphasis should be placed on the synergism of a complicating disease and a chronically poor state of metabolic regulation. Also, it is necessary to expose the fallacy that the latter necessarily reflects itself in subjective symptoms or in a fasting (rather than two-hour postprandial) urine test in the face of the usually elevated renal threshold. In effect, the emphasis should be shifted to the need for periodic medical observation and blood sugar determinations.

Finally, with regard to peripheral vascular complications, the patient should be given definite written instructions regarding foot care, and the dangers of self-

surgery and self-medication should be clearly underlined.

SUMMARY

Education about diabetes does not consist simply in presenting the basic facts to patients. Rather, it should be directed to a real understanding of the disease and a proper attitude toward its care by both patient and physician. A more precise definition of the area for which the patient is responsible will prevent both his overstepping the bounds or, even worse, ending up completely outside medical supervision. It is entirely reasonable to propose that good medical care of each hospitalized diabetic regardless of the cause of admission is not complete until he has been educated in self-care. The responsibility for this program in the hospital should properly rest upon both the administrative and professional staffs, with the understanding that patient education is a vital facet of the minimum standards of medical care in their institution.

SUMMARIO IN INTERLINGUA

Inseniamento del Patiente Diabetic

Le education del diabetico non se exhauri in presentar a ille le factos fundamental del morbo e de su tractamento. Le objectivo de tal education debe esser le' disveloppamento de un ver comprehension del morbo e de un appropriate attitude verso su manipulation non solmente del parte del patiente sed etiam del parte del medico. Un plus precise definition del area pro que le patiente es responsabile va prevenir transgressiones e—lo que es ancora multo plus importante—le complete escappamento del patiente a omne supervision medical. Il es integremente rationabile insister que le tractamento medical del hospitalisate diabetico individual (sin reguardo al causa de su admission al hospital) non es complete usque ille es ben educate in su deberes autophylactic. Le responsabilitate pro un tal programma educative in le hospital es justemente un carga del personal tanto professional como etiam administrative. Il debe esser comprendite que le education del patiente es un aspecto vital del standards minimal de sollicitude medical in nostre institutiones.

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Old Age is a State of Mind

In summary, one might briefly outline some of the main needs of the older person as follows:

1. A chance to be useful, creatively productive.
2. A chance to be active.
3. The need to be loved or wanted.
4. The need for financial security.
5. A chance to be a free human being.

In order that these things may accrue to him, the senior citizen has certain tasks for which he alone can be responsible. Briefly these are as follows:

1. To learn to adjust to declining physical capacity.
2. To learn to compensate for loss of friends and family as inevitable death removes them from the scene.
3. To learn to live happily in spite of reduced income, loss of social status due to loss of useful, respected role in society.
4. To learn to utilize effectively increased leisure.
5. To develop a basic philosophy toward life for later years.

In amplifying this last statement there should be some discussion of the religious implications involved. If we induce our senior citizens to believe that all change and advancement in life are perfectly timed, perfectly tuned, and harmonized in divine order and good will, they may find the adjustment to advancing years not too difficult to make.

After all, old age is just a state of mind. The philosophy of the candle might prove an inspiration to many an oldster. This couplet, the source of which escapes me, is as follows:

I'll soon be dead, the candle said.
I, inch by inch, decline.
But I make light of my sad plight
For while I live, I shine.

H. A. Steckel, M.D., from "Emotional Aspects of the Aging Process," *New York State Journal of Medicine* 55:3605-06, Dec. 15, 1955.

EDITORIALS

TWINS AND DIABETES MELLITUS

There is increasing recognition of the fact that the expression of a tendency to a genetically determined disease, such as diabetes, may depend upon environmental factors.[1] It seems worth-while to emphasize that discordant monozygotic twins, a type often neglected in twin studies, furnish valuable evidence of the complex etiology of diabetes.

Long ago Galton suggested the study of twins as a method for the separation of hereditary and environmental influences in the development of human traits. Subsequently, twins have been studied extensively in research on the etiology of many diseases. The striking similarities (concordance) of monozygotic twins in physiological and pathological characteristics are usually compared with the similarities or dissimilarities of dizygotic twins in order to distinguish between genetic and nongenetic determination of the traits in question. Such comparisons have been made repeatedly among diabetic twins, both mono- and dizygotic. Joslin *et al.*[2] pointed out that, if diabetes is inherited, the incidence of the disease in both members of pairs of monozygotic twins should far exceed the incidence in dizygotic twins. Such an excess of monozygotic twins concordant with regard to diabetes has been demonstrated in several surveys[2, 3, 4, 5, 6, 7] thus giving support to the view that genetic factors play an important role in the etiology of diabetes.

Although in many instances both monozygotic twins develop diabetes, important exceptions have been reported. In a series observed by Joslin *et al.*[2] there were 33 sets of monozygotic twins. Of these both members were diabetic in only 16 pairs or 48.5 per cent, while 17 or 51.5 per cent were discordant when the study was made. Discordant monozygotic twins were also encountered by other observers.[4, 5, 7]

It is true that in the nondiabetic members of such monozygotic pairs a tendency to the disease is often demonstrable by glucose tolerance tests and that the member who is healthy at the time of the survey often develops diabetes in later life.[4, 5] In other words, one member of the pair may have the overt disease while the other has it in a latent form. Since it is a very different matter to the patient whether he has merely a genetic tendency to the disease or whether he suffers from diabetes and all its consequences, knowledge of the factors that convert an inherited latent tendency into frank diabetes would be of great practical importance. In case of discordance in the members of a pair of monozygotic twins, who by definition have the same genetic constitution, *nongenetic* factors must determine the development of a disease that appears in only one. It is important, therefore, to study not only concordant monozygotic twins but also discordant ones, who can, under favorable conditions, improve our knowledge of nonhereditary pathogenic factors.

A recent report of discordant monozygotic twin brothers[8] is of special interest, because one of the twins became diabetic in his eighth year, while the other twin remained free of the disease for at least seventeen years after the onset in his brother. Moreover, the nondiabetic brother showed a pronounced tendency to obesity, while the diabetic twin remained thin and wiry. The glucose tolerance tests of the nondiabetic twin yielded blood sugar curves within normal limits. The family history revealed that diabetes as well as obesity had occurred in relatives; therefore one can assume that the twins could have inherited a tendency to both diabetes and obesity. Inquiries made to ascertain what environmental influences might have made one of the twins diabetic and the other obese were not fruitful. The twins grew up in the same household and were exposed to the same environmental influences. The mother stated that the appetites of the twins were similar and never excessive during childhood. There was a history of a severe attack of pertussis with severe symptoms in the diabetic brother and of pertussis with milder symptoms in his twin; but the record left some uncertainty whether this episode preceded the onset of diabetes or immediately followed it. Thus no decisive event could be discovered in retrospect which might account for the discordance.

In some cases discordance with regard to diabetes can be explained, at least tentatively, by precipitating factors such as alcoholism,[6] infections,[5, 7] or repeated pregnancies[4, 7] in the affected twin. The last factor of course applies to adult females only. In the majority of cases, however, the decisive nongenetic factors cannot be ascertained.[5, 8] Such observations indicate that environmental factors, which convert an inherited tendency to diabetes to the manifest disease, may be much more subtle and evasive than is usually assumed.

Some of the cases of discordant monozygotic twins are of interest also because they throw some light on the relationship of obesity to diabetes. In 1938 Lemser[4] reported a pair of twins, one undernourished with diabetes, and one obese and free of diabetes, though showing decreased glucose tolerance. These twins were adult women when examined. The diabetic sister had been in poor economic circumstances and had undergone ten pregnancies. The nondiabetic sister could afford ample food and had only one pregnancy. In the twins recently reported,[8] who became discordant in childhood, the obese twin remained free of diabetes, while the lean one developed the disease. If the reverse had been true, overeating and obesity would have been considered by some as an accessory diabetogenic factor. There can be little doubt that some relationship exists between obesity and diabetes, especially in later years, but that does not mean necessarily that this relationship is a causal one. Some observations on twins,[4, 8] seem to indicate that obesity and diabetes sometimes may be parallel phenomena and not cause and effect.

Discordant monozygotic twins represent rare experiments of nature which can be of great value in etiologic research on diabetes and other diseases. Observations of concordant monozygotic twins with diabetes who differ in respect to various complications should also be highly informative. Sometimes such studies of a few exceptional cases may be more rewarding and less expensive than large-scale statistical research.

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FRIEDENWALD'S CONTRIBUTION TO KNOWLEDGE OF DIABETIC RETINOPATHY

The unsolved problem of diabetic retinopathy has received increasing attention in recent years. Interest has been stimulated by the rising incidence of this disabling complication and by recent progress in our understanding of the nature of the disease process. During the last ten years of his life, the efforts of Jonas Friedenwald provided the solid background and inspiration for much of the current work and many of the present concepts about the pathology and pathogenesis of diabetic retinopathy.

The ophthalmoscopic picture of diabetic retinopathy was clearly defined by Jaeger in 1855. In 1877 MacKenzie and Nettleship described the nature of the aneurysmal capillary disorder of the retina which accounted for the clinical picture. Unfortunately, this fine work was not generally accepted until its rediscovery by Ballantyne and Loewenstein in 1943.

In the course of the routine application of histochemical technics to ocular tissues, an intensive study of the mucopolysaccharides of the eye was undertaken by Friedenwald and co-workers in 1946. When Hotchkiss described the periodic-acid-fuchsin method for staining polysaccharides in fixed tissues, the procedure was modified in Friedenwald's laboratory for application to sections of human eyes. It became apparent upon examination of the very first sections that the basement membranes of the retinal vessels stained brilliantly. The application of this staining technic to flat preparations of the retina provided a most useful method for the microscopic study of its entire vascular tree. New light was thus shed upon the intimate nature of retinal vascular diseases. When retinas of diabetic patients were examined, a most impressive demonstration was afforded

of the innumerable capillary aneurysms that characterize diabetic retinopathy. Furthermore, the relationship of the aneurysms to the surrounding hemorrhages and exudates became apparent. Available for study in minute detail was the life history of the capillary aneurysm. In single specimens one could trace the development from a thin-walled dilatation to an onion-skin lamellated polysaccharide mass, which ultimately became hyalinized.

Friedenwald then undertook the study of the application of periodic-acid-fuchsin technic to other organs of diabetic patients. This resulted in the finding of similar staining and lamellation of the globular renal glomerular masses, previously described by Kimmelstiel and Wilson. In addition, serial sections of kidneys revealed true capillary aneurysms in the glomeruli of patients with retinopathy. A review of a large number of diabetics at autopsy revealed the occurrence of renal lesions only in those diabetics who had retinopathy. Thus were correlated for the first time the renal and retinal lesions of the diabetic, both as to appearance, staining characteristics, and occurrence in the same individuals.

Under the direction of Friedenwald, efforts were then concentrated on a comparison of the differences between diabetics with and without retinopathy. Thus was begun an intensive clinical and laboratory investigation in diverse directions and encompassing many related fields. Studies were undertaken of possible alterations in serum polysaccharides, plasma proteins, acetylating capacity, xanthurenic acid excretion following tryptophane administration, urinary vitamin B-12 output after parenteral administration, 17-hydroxysteroid excretion, eosinopenia following ACTH, etc. In addition, the studies of pathologic differences were continued and numerous attempts were made at experimental production in animals. From these extensive efforts the hypothesis which emerged that best accounted for the available clinical, histo-pathologic, and experimental data was that the adrenal cortex might play a role in the pathogenesis of diabetic retinopathy and nephropathy. Although this thesis remains unproved, subsequent studies and experiments have offered no outstanding evidence that negates the role of adrenocortical dysfunction in this disease process. This working hypothesis has provided a basis for various productive research projects. The perplexing problem of diabetic retinopathy remains unsolved, but there is every indication that its ultimate resolution will rest upon the solid foundation afforded by the brilliant work, the uncanny insight, and the stimulating suggestions of Jonas Friedenwald.

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MEDICAL RESEARCH: A MIDCENTURY SURVEY

The advent of two volumes under the above title invites editorial comment in appreciation and commendation of an invaluable critique of a half century of research in the medical sciences. A full awareness of the significance of these volumes requires a glance backward to the status of medical research in 1900.

At the turn of the century, scientific advance in the field of medicine proceeded at a snail's pace. What advances were being made were accomplished chiefly in the medical schools. The greatest experimental activities were in laboratories associated with departments of pathology. Here interest centered around morphology and the relations to basic sciences were either tenuous or nonexistent. Pharmacology was mainly materia medica and bacteriology was a new and essentially unexplored science which as yet had not penetrated appreciably into the medical schools. Clinical medicine was taught by busy practitioners and what experimental medicine they engaged in was largely confined to bedside observation, chiefly on the effects of therapeutic measures.

Now at the midcentury mark, the picture of the state of medical research is dramatic in its antithesis to that presented in 1900. Medical science is advancing at an ever accelerating rate. The basic sciences of chemistry, physics, and mathematics are assiduously mined for fundamental concepts which will lead to a better comprehension of the problems of disease. Not only in medical schools but also in independent foundations, large and small, and in the laboratories of innumerable pharmaceutical houses, research workers are pouring forth continually a torrent of literature on every aspect of medical science. The medical schools, both in the preclinical and clinical branches, are now staffed by men highly trained in many areas of the basic sciences. The lecture halls and clinics are flanked by numerous laboratories filled with elaborate and costly apparatus, manned by highly skilled technicians. These laboratories are constantly seeking to recruit to their staffs young men trained in basic sciences who are initiating careers in all areas of clinical medicine.

Financial support for medical research from government, private foundations, and from the public through the large national societies totals millions of dollars per year. Thousands of research projects directed by competent investigators are now supported by such foundations. Most individuals who have demonstrated reasonable competency in medical research can obtain adequate financial aid for investigative work in any direc-

tion which they believe will be rewarding. Fifty years of such activity has brought about enormous advances which have contributed immeasurably to our knowledge of disease.

The year 1950 afforded an appropriate time for a survey by competent persons of the many factors, scientific and otherwise, which contributed to these advances. This The American Foundation in *Medical Research: A Midcentury Survey** has done. In these volumes is presented an exposition of research progress in medical science for the past fifty years together with an evaluation of its significance. The magnitude of this task is indeed formidable, and it has been approached with vigor and understanding. For the accomplishment of the present task, the Foundation assembled a committee of consultants who are outstanding authorities in many fields associated with medical research. The members of this committee furnished the basic factual materials upon which the exposition and evaluations were made. But without coordination and integration, these reports would have lost much of their cogency and force. Miss Esther Everett Lape, the Foundation's "Member in Charge," and her staff have furnished these integrating and coordinating factors which make the *Survey* one of outstanding merit.

The first volume concerns itself with "American Medical Research in Principle and Practice." An introductory chapter outlines the scope of the "Survey." There follows an exposition of the relationship of the contributions of the fundamental sciences, chemistry, physics, and mathematics, to biological research. The rest of the volume expands a detailed discussion of the sociological, the financial, and the political factors which bear upon the manifold problems arising in the advancement of research in the medical sciences.

This volume, while perhaps more appealing to those concerned with administrative problems in medical education, medical research, medical care and other medical problems of public or quasi-public nature, is nevertheless highly informative and stimulating to those who are desirous of understanding the manifold factors which are involved in the administration of public policies in medical science.

Of particular interest to the practicing physician is the second volume, *Unsolved Clinical Problems in Biological Perspectives,* which presents a discussion of nine such problems. These are: cancer, infertility, arteriosclerosis, hypertension, the rheumatic syndrome, tuberculosis, the nature of virus and virus diseases, alcoholism, and schizophrenia. In these chapters, the advances of a half century of research in the respective fields together with an exposition of the current status of these problems are given in most succinct form without inclusion of distracting technical details or masses of experimental evidence. Indeed, as reviews of these complex subjects, they are examples of masterly thoroughness combined with unusual brevity.

The introductory chapter of this volume, "Current Metabolic Concepts Orienting Research in Biology and Medicine," is of particular interest to those concerned with diabetes or other clinical conditions involving metabolic concepts. Here the emphasis is upon basic principles: "Normal physiological functions are manifestations of the molecular changes that are metabolism; disease is a constellation of disturbances of finely integrated chemical mechanisms." The emphasis continually is that comprehension of symptoms and manifestations in disease must presuppose the understanding of molecular mechanisms which underlie biological activity. The role of enzymes and coenzymes is developed leading to discussion of the diversities of cellular metabolism. Cellular homeostasis is discussed in terms of these complex enzyme reactions. The relation of these reactions to the production of stored chemical energy as energy-rich phosphate compounds by oxidative phosphorylation is brought out. Finally the interrelation of the pancreatic islands, the pituitary, the adrenal, and other hormonal organs to these complex processes is outlined to the extent to which they are known. The chapter is illuminating in its discussion of how possible aberrations of these complex interrelationships of enzymes, coenzymes, and hormones leads to the development of diabetes mellitus. "The picture of diabetes as a syndrome involving defects in some aspect of nearly all phases of cellular metabolism and of the coordinating mechanisms of hormone interrelations is incomplete, suggesting many discrepancies. In nature there are no discrepancies and those that appear in tentative formulations therefore represent either erroneous observation or incomplete information. We may hope that, when all the facts are in, the apparent discrepancies will be resolved."

The chapter on alcoholism presents an analysis of a difficult problem in which many conflicting facts and opinions are placed in balanced perspective. In particular, the metabolic, endocrinologic, psychologic, and psychiatric aspects of this problem are discussed in the light of evidence both in humans and in animals which

**Medical Research: A Midcentury Survey,* Volume I, 765 pp; Volume II, 740 pp. Boston, Little, Brown and Co., for The American Foundation.

have significant bearing on these facets of the problem. There is an illuminating discussion of the hypothesis that the compulsive drinker develops a conditioned pattern of tissue enzyme activity which forms the basis for his habituation. The craving for alcohol is explained "in terms of genetically conditioned individual biochemical differences that produce a relatively heightened need for vitamins or other elements." The evidence for this in the opinion of one authority is "clear-cut and unequivocal." In the opinion of another, however, the summation of the experimental evidence is "considered to be incompatible with any narrow concept of human alcoholism as due to nutritional or genetotrophic defects." And another authority concludes that such a hypothesis is not applicable to "the intricate problem of human alcoholism without a great many further fundamental investigations."

The remaining chapters of this volume are also treated with clarity and brevity. They comprise model reviews for the reader who wishes to keep abreast of these advancing fronts of medicine. Emphasis is constantly upon fundamentals, and metabolic aspects of these perplexing clinical problems come in for their share of emphasis. No one who aspires to the acquirement of some degree of scholarly purview of the entire field of medical science can afford not to possess and study these two books.

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The Quality of Value

No one has yet discovered a way of cultivating inventive genius. Psychologists who have been working on the problem for many years are not encouraged, in spite of the fact that some men have seemed to have an extraordinary capacity to inspire others to achievement. How do they do it? Perhaps this should be a prime target for pedagogic research, but a distinction should be made between originality and invention. Invention may be defined (for our purpose) as originality with a quality of value, whether applied to music, design, or science. It is a simple matter to teach originality if the quality of value is left out. Perhaps a starting point might be an attempt to develop men who regard their work as a fascinating adventure—a perpetual series of expeditions into the unknown. The conventional technologist has a different viewpoint. He is skeptical of the very existence of the unknown, and he lacks the emotional drive to achievement of capital invention. Unless a man can be swayed by fancies he will stay with his facts and will never make the trips. We must try to develop imaginative men who can conceive of the unknown places, who have the naïveté to believe in their existence, the daring to start into the wilderness, and the stubborn determination to stay there until they can depart with some of its riches. If it is possible to teach genius, instead of merely hoping it will come along, the future will belong to the society that first discovers how.

From "Social Attitude Toward Invention"
by Eugene Ayres in *American Scientist* 40:
521-40, October 1955.

Psychological Factors in the Scientific Process

It is commonplace to say that science depends on communication, that the invention of printing eventually advanced science enormously, that the publication of results is always essential, that the iron curtain and the secret classification of data are bad for science. All such obvious statements are concerned with whether or not the normal overt mechanisms of communications are working or blocked. On the other hand, there are covert influences that make up what has been called the climate of opinion, and by Goethe the *Zeitgeist*—the conventions of thought and the unquestioned assumptions that are implicit in the culture in general and in science in particular. These forces act as *vires inertiae*. They constrain originality and reinforce tradition, as well as limiting the irresponsibility of the cranks who, excelling in originality, are deficient in critical wisdom. Conant has remarked that "a scientific discovery must fit the times . . . A well-established concept may prove a barrier to the acceptance of a new one. If a conceptual scheme is highly satisfactory to those who use it, neither a few old facts which cannot be reconciled nor a few new ones will cause the concept to be abandoned . . . Old concepts may be retained in spite of alleged facts to the contrary." The *horror vacui* that science cannot deny is the scientist's fear of being left without any theory at all. "It takes a new conceptual scheme to cause the abandonment of an old."

Edwin G. Boring in *American*
Scientist 42:639-45, October 1954.

Jonas Stein Friedenwald

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The untimely death of Dr. Jonas Stein Friedenwald occurred on Nov. 5, 1955, after a comparatively short illness. His passing is undoubtedly one of the greatest losses to medicine today. His stated specialty was ophthalmology but his interests extended into many other fields of medicine and science. He was especially interested in vascular abnormalities associated with diabetes. He served with distinction on the Editorial Board of this Journal from its inception until his death.

Dr. Friedenwald was a member of a prominent Baltimore family whose interest in medicine extends back three generations. His grandfather, Dr. Aaron Friedenwald, was Professor of Ophthalmology at the College of Physicians and Surgeons in Baltimore from 1873 until his death in 1903. His father, Dr. Harry Friedenwald, held the Chair of Ophthalmology at the same college from 1902 until it merged with the University of Maryland in 1915. He then became Professor of Ophthalmology at the University of Maryland. Dr. Harry Friedenwald was not only internationally known in his specialty of ophthalmology, but he was also a noted medical historian and wrote many articles on the contributions of Jews to medicine.

With this rich heritage Jonas Stein Friedenwald was born on June 1, 1897. He received his early formal education at Calvert and Friends schools and entered The Johns Hopkins University in 1913 and was graduated with honors in 1916. He then entered The Johns Hopkins University School of Medicine and was graduated with a distinguished record in 1920. Thereafter, he served for a year as a house officer in medicine in The Johns Hopkins Hospital and in 1921-22 studied pathology of the eye at Harvard University under Dr. Frederick Verhoeff. He then went to Philadelphia for a year where he worked under Dr. deSchweinitz. In 1923 he returned to Baltimore and entered the practice of ophthalmology with his father. During the same year he was appointed Instructor in Ophthalmic Pathology, a subdepartment of the Department of Pathology of The Johns Hopkins University School of Medicine under Dr. George MacCallum. With the founding of the Wilmer Institute in 1925, Dr. Friedenwald was appointed Instructor in Ophthalmology in charge of the pathology laboratory. In 1929 he was appointed Associate in Ophthalmology and in 1931 Associate Professor, a position which he held until his death.

Environment and heritage greatly influenced Jonas Friedenwald to begin the extensive study of the scientific aspects of medicine in which field he became so famous. The Friedenwald house at 1212 Eutaw Place was both his father's home and office. Here many of the great men of medicine often gathered to listen to a visiting scholar or to examine and to review some of the rare books and manuscripts in his father's private collection.

Dr. Friedenwald, during his active professional life, made almost 200 scientific contributions to the literature. It is interesting to review their sequence. They began with descriptions of histopathological abnormalities and clinical syndromes. They then passed to problems in optics related to the ophthalmoscope and slitlamp, then on to biochemistry. His book on ophthalmic pathology written when he was only 30 years of age and published in 1928 was required reading for most young ophthalmologists. In 1952, in conjunction with others, he revised and greatly expanded this publication. There is little doubt that Dr. Friedenwald was one of the greatest ophthalmic pathologists of his time. His studies on the dynamics of aqueous flow in the eye will go down as classics of meticulous systematic investigation of a difficult problem. His works in this field have done more than any other investigator's to solve the problem of glaucoma. Through all of his experimental work and in his publications he made use of his background in mathematics. Thus he wrote on such diverse works as "Population Growth in Palestine," "Calibration of the Tonometer," "Knowledge of Space Perception in the Portrayal of

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Depth in Painting," "Elementary Kinetic Theory of Enzymatic Activity," and "Some Implications of Modern Physics for the Biologic and Social Sciences."

Among his many and varied investigations the problem of diabetic retinopathy was one which was of special interest to Dr. Friedenwald. Characteristically, his approach was broader than clinical. His extensive knowledge of histopathology, biochemistry, and physiology was applied not only to retinopathy per se, but to the investigation of the general metabolic disorders which occur in diabetes mellitus.

His work on the pathologic aspects of this disease and the technics which he developed were instrumental in differentiating between the retinal lesions of diabetes and those of other retinopathies. These studies defined a specific ophthalmoscopic, as well as pathologic picture, of diabetic retinopathy. His contributions were of great value in pointing out the relationship of the Kimmelstiel-Wilson renal lesions to the vascular lesions of the retina.

At the time of his death, one of Dr. Friedenwald's major research projects was an investigation of the relation of adrenal cortical secretion to vascular complications in diabetes. He postulated an interaction between adrenal cortical function and the vascular lesions of the retina and kidney. In addition to investigating adrenal cortical activity in diabetics with and without retinopathy, as well as in experimental animals, he further elaborated this theory by directing his attention to the effect of cortisone on mucoid metabolism.

To quote from one of Dr. Friedenwald's papers, "It would appear that the happy and exciting threshold has been reached at which specific and potentially answerable questions can be formulated regarding the pathogenesis and etiology of this vascular disease."

His monographs will always be classics in this field and he will remain not only as a stimulus for further investigation, but as the foundation upon which the ultimate solution of this problem rests.

The tabulation of specific contributions made by this great investigator could go on and on, but it would not adequately depict the calm and usually mild-mannered man who at times could be alarmingly stern or bitingly sarcastic if provoked beyond all reason. In spite of the tremendous amount that he was able to accomplish, he never appeared rushed, and always had time to sit and chat with a truly interested neophyte in the field of medicine or other branch of science. His enormous fund of knowledge and experiences were sought equally by students, residents, clinicians, and research men in various fields both at Hopkins and throughout the country. He could discuss on equal terms with top-flight specialists many complex phases of both science and clinical medicine.

He was also keenly concerned about world affairs and profoundly interested in the development of Israel. On several occasions he went to Jerusalem to assist in the planning and development of the medical school and hospital of Hadassah.

Dr. Friedenwald's achievements were frequently recognized during his lifetime. He received the Research Medal of the American Medical Association in 1935, the Proctor Award in 1948, the Lucien Howe Medal of the American Ophthalmological Society in 1951, and the Donders Medal of the Dutch Ophthalmological Society in 1952. In the spring of this year he was to have given the Doyne Lecture before the Oxford Ophthalmological Congress as his father had in 1931. His keen scientific mind, complete honesty, and understanding of his fellow man made him a frequent counselor on important committee posts. He was a member of the Council of Neurological Diseases and Blindness, a counselor for the Hadassah Hospital and Medical School in Israel, a member of the Committee on the Standardization of Tonometry, Radiation Cataract Committee, and many other local and national committees. He was a member of the Editorial Board of the AMA *Archives of Ophthalmology, Ophthalmologica* and *Journal of Histochemistry and Cytochemistry.*

With all these activities Dr. Friedenwald was still able to carry on an active private practice in ophthalmology. Most of his clinical observations and evaluations were based on patients seen in his private practice and on the records of his father's patients. He was a kind, sympathetic, and painstaking physician, and was greatly loved by his many faithful patients.

In 1925 he married Marie Louise Sherwin, a nurse of The Johns Hopkins Hospital, whom he had met while he was on the house staff of the Osler medical service. Their marriage was one of perfect understanding and companionship. There is no doubt that Dr. Friedenwald's vast accomplishments would have been greatly curtailed had it not been for Mrs. Friedenwald's complete devotion to him and to his interest in science.

The loss of such a man as Jonas S. Friedenwald is always a most sorrowful happening, but this is particularly true when it occurs to a man in his prime of 58 years. His accomplishments were great by any standards, but had he lived another ten or fifteen years, they would have increased many fold for his knowledge of chemistry and mathematics was increasing each year, and its application was becoming more obvious to each new problem he undertook.

ABSTRACTS

Abrahamson, E. M.: THE GLUCOSE HOMEOSTASIS TEST. Am. J. Digest. Dis. *22*:267-71, September 1955.

The author suggests the term "glucose homeostasis test" for the six-hour glucose tolerance test for functional hyperinsulinism. This would avoid confusion with the glucose tolerance test for diabetes, which is done for a shorter period of time. It is suggested that the glucose homeostasis test be done with arterial blood, because the difference in glucose levels between venous and arterial blood in hyperinsulinism is significant because of tissue absorption of glucose. In diabetes, the difference is not significant because of the impairment of the ability of the tissues to absorb glucose; therefore, venous blood can be used satisfactorily for glucose tolerance tests.

It was stressed that methods of analysis should give *true* blood sugar. A modification of the Folin-Wu method was suggested and described in detail.

Alvarez, Luis María; Pupi, Roberto Edmundo; and Raffaele, José Francisco: LENTE INSULINS IN THE TREATMENT OF DIABETES. Semana méd. *107*:109-15, July 21, 1955.

The three types of insulin, Semilente, Ultralente, and Lente, were studied in a series of 30 female diabetic patients. In accordance with this experience, these insulins are indicated in mild diabetes, the Lente insulin being the most suitable for these cases. These insulin-zinc suspensions are not advisable in labile or brittle diabetes. In severe diabetics, the results with these insulins were far below those obtained with mixtures of insulins. No allergic reactions were noted with these insulins. (Spanish)

Baumgartner, Conrad J.; and Reynolds, John L.: FUNCTIONING METASTASES FROM ISLET-CELL TUMOR OF THE PANCREAS. CONTROL WITH CORTICOTROPIN (ACTH). A.M.A. Arch. Surg. 70:793-800, June 1955.

The authors present a case of islet-cell tumor of the pancreas with functioning metastases, with several unique observations. The metastases functioned at a time when the primary lesion, from a clinical standpoint, was apparently nonfunctioning. The patient developed a duodenal ulcer with the onset of hypoglycemia, which was apparently due to hyperchlorhydria produced by hyperinsulinism. The authors indicate that the case is the first to be recorded in which the hypoglycemia from a functioning metastatic islet-cell tumor has been controlled for a period of one year by ACTH.

Bounds, G. W., Jr.; Janes, R. G.; and Leinfelder, P. J.: CATARACTS INDUCED BY ALLOXAN DIABETES IN RATS AND RABBITS. EXPERIMENTAL STUDIES. A.M.A. Arch. Ophth. 54:564-72, October 1955.

An ophthalmoscopic and histologic study of cataracts caused by alloxan diabetes in the rat and rabbit is presented. The formation and progression of diabetic cataract were observed in relation to the severity of the diabetes. The addition of nicotinic acid, the injection of cysteine, and the maintenance of rats in an atmosphere of 38 to 40 per cent oxygen were not found to alter the progression of a cataract in alloxan-diabetic rats.

Burt, Richard L.: PERIPHERAL UTILIZATION OF GLUCOSE IN PREGNANCY. II. PRE-ECLAMPSIA. Obst. & Gynec. *6*:51-54, July 1955.

The authors performed intravenous glucose tolerance tests in 13 patients with pre-eclampsia. As compared with the response in normal pregnancy, the blood glucose concentrations were higher and the serum inorganic phosphorus concentration unchanged in pre-eclampsia. It is suggested that altered hepatic function in toxemia may be responsible for the findings.

Clement, Robert: GLUCAGON, A HYPERGLYCEMIC, GLYCOGENOLYTIC HORMONE OF THE PANCREAS. Presse méd. *63*:746-48, May 18, 1955.

Glucagon, secreted by the alpha cells of the pancreas, induced a rise of the blood sugar level at the expense of the liver glycogen. Its secretion is stimulated by hypoglycemic conditions and, therefore, by insulin; it is also stimulated by the pituitary growth hormone. In certain hypoglycemic conditions, a diminution in number or an aplasia of the alpha cells of the pancreas was observed; it is not unlikely that a deficiency in glucagon might be the cause of some hypoglycemic states. (French)

Cole, B. Theodore; Engel, Frank L.; and Fredericks, Joan: SODIUM FLUOROACETATE DIABETES: CORRELATIONS BETWEEN GLYCEMIA, KETONEMIA AND TISSUE CITRATE LEVELS. Endocrinology 56:675-83, June 1955.

Hyperglycemia persisted from 40 to 64 hours and ketosis from 24 to 40 hours in fasted and fed rats following the intraperitoneal injection of sodium fluoroacetate. Tissue citrate accumulation in certain tissues paralleled the diabetic findings. The findings were taken to indicate that fluoroacetate poisoning by blocking the Krebs citric acid cycle resulted in diabetes in these animals.

Colwell, Arthur R.: SELECTION OF THERAPY IN DIABETES MELLITUS. M. Clin. North America, pp. 39-55, January 1955.

The author discusses the different forms of therapy in diabetes according to the severity of the cases. He points out the difficulties that are encountered in maintaining normal nutrition and metabolic conditions as the severity of the diabetes increases, and he stresses the point that the more severe the diabetes the more individualized the treatment that becomes necessary. He presents five illustrative cases of varying degrees of severity and the most appropriate methods of treatment in each.

Constam, G. R.: EXPERIENCES WITH INSULIN-ZINC SUSPENSIONS, A GROUP OF INSULIN PREPARATIONS (LENTE INSULINS) WITH DIFFERENT DURATION OF ACTION. Schweiz. med. Wchnschr. *84*:200-04, February 6, 1954.

Satisfactory results were obtained in the treatment of medium to severe cases of diabetes mellitus. Semilente insulin was more frequently used than Lente insulin. Of 50 diabetics, only 4 were treated with Ultralente insulin. Some patients showed skin reactions at the site of injection. Headache is the most frequent subjective symptom of hypoglycemia due to insulin-zinc suspensions. (German)

Constam, G. R.; Hochstrasser, P.; and Rosenbusch, H.: A SWISS CAMP FOR DIABETIC CHILDREN. Schweiz. med. Wchnschr. *84*:377-78, March 27, 1954.

This article reports the purpose, the organization, and the result of a camp for diabetic children. (German)

Constam, G. R.; Hochstrasser, P.; and von Sinner, F.: ABOUT THE PROGNOSIS OF DIABETES MELLITUS. Schweiz. med. Wchnschr. *84*:1233-39, October 30, 1954.

Complications of diabetes are diseases which occur together with diabetes mellitus but which have no pathogenic relations to it. In opposition to this, vascular changes and others which develop after many years of diabetes and which seem to be the consequence of it are called, according to Lundbaek, diabetic late symptoms.

One hundred and three diabetics were examined for late symptoms 20 years after the first manifestation of disease. About 1/5 of them had no late symptoms; 1/5 had a few, and 3/5 had many of the symptoms. The age of the patient and the quality of treatment were the factors which influenced the development of late symptoms and not the severity of diabetes or the kind of insulin which was used. Of 21 diabetics "with constant good control," only 1 patient had many, 9 few, and 11 no late symptoms; whereas of 32 diabetics with "constant poor control," 2 alone were free of late symptoms, and 2 had few of them.

Among 117 diabetics who were observed 20 and more years after the first manifestation of their disease, there were four who had such mild diabetes that very few food restrictions were sufficient to keep it well controlled from 20 to 50 years. In spite of these rare exceptions, for the vast majority of diabetics, early and optimal control offer the best chances to avoid or at least to postpone late symptoms for many years. These observations emphasize the great responsibility of the physician who treats diabetics. (German)

Constam, G. R.; and Schmid, H.: IS HONEY RECOMMENDABLE FOR DIABETES? Schweiz. med. Wchnschr. *85*:282-83, March 19, 1955.

Since some physicians as well as lay people recommend honey for diabetics, the authors have compared the blood sugar curves and urine sugar eliminations in 4 diabetics and a nondiabetic after a breakfast with and one without honey.

The addition of honey increased the post-alimentary hyperglycemia and glycosuria in 3 of the 4 diabetics. In one, the glycosuria was increased, but the hyperglycemia remained unaltered. In the nondiabetic, the addition of honey did not change the post-alimentary hyperglycemia. Honey is therefore not recommended as a part of the regular diet for diabetics. (German)

Covelli, Juan Roberto; and Carlomagno, Alfredo P.: DIABETES AND LIVER DISEASES. Día méd. *27*:1786-91, August 11, 1955.

The disappearance of hepatomegaly, along with the decrease of blood lipids to normal after the treatment of uncontrolled diabetics by insulin and diet, has been described. The favorable role of amino acids in the correction of abnormal fat metabolism in diabetic patients has also been described. Lipotrophic factors have been used for this problem. In diabetic patients showing a high blood lipid level, it is advisable to administer lipotrophic factors along with a low-fat diet. This would prevent not only the fatty infiltration of the liver but also the degenerative vascular changes. (Spanish)

Dische, Zacharias; and Zelmanes, Ginevra: POLYSACCHARIDES OF THE VITREOUS FIBERS. A.M.A. Arch. Ophth. *54*:528-38, October 1955.

The particulate matter of the frozen and thawed-out vitreous consists of up to 90 or 95 per cent of a fibrous material that can be quantitatively extracted by 5 per cent TCA at 90°C. in 20 minutes. These fibers are combined with one or several polysaccharides which contain glucose and galactose in nearly equivalent

amounts and much smaller amounts of an unidentified hexosamine. In addition, a certain amount of a polyuronide is loosely attached to the fibrous material and can be separated from it by incubation with hyaluronidase. The vitreous contains a small amount of a soluble glycoprotein, which becomes insoluble by freezing at —15°C. and is precipitated with the fibers. The possible significance of these findings for the problem of the polysaccharide moiety of collagen fibers is discussed.

Downie, Ewen: THE CLINICAL APPROACH TO THE PROBLEM OF DIABETES MELLITUS. Brit. M. J. *2*:863-67, October 8, 1955.

The paper represents the Banting Lecture delivered at the University of Toronto on May 16, 1955. The lecturer feels that there is more of a dynamic aspect to the diabetic state than is appreciated. There is a need for long-term studies on the genetics of patients with fluctuating diabetes.

Drucker, William R.; Costley, Christine; Stults, Robert; Gross, Gilbert; Holden, William; Miller, Max; Craig, James; and Woodward, Hiram: THE EFFECT OF ANESTHESIA ON INTERMEDIARY CARBOHYDRATE METABOLISM. Clin. Res. Proc. *3*:202-03, November 1955.

Previous studies indicate that glucose tolerance is decreased during stress, whereas fructose tolerance is unchanged. These changes have been interpreted as being due to blocks of specific enzymatic processes. In this study, patients were given 3 daily glucose or fructose tolerance tests: one before, one during, and one after anesthesia. No consistent alterations occurred in either glucose or fructose tolerance with Pentothal.® However, decrease in glucose tolerance occurred when ether was used, either alone or with Pentothal.® Little alteration was found in fructose tolerance with ether. Serum inorganic phosphate usually rose during ether anesthesia—a finding different from that seen with tolerance tests after other types of stress.

Editorial: DIABETES MELLITUS IN INFANCY. Brit. M. J. *2*:956-57, October 15, 1955.

Diabetes mellitus in infancy is discussed. The diagnosis may be made shortly after birth. The disease may be transient and even disappear, then reappear in later years. It is doubtful if diabetes has ever been "cured."

Editorial: HYPERGLYCAEMIA AND VISUAL DISTURBANCES. Brit. M. J. *2*:427, August 13, 1955.

The relationship between transient visual disturbance and hyperglycemia is well known. The findings of Verel are quoted, wherein he describes a diminution of the ophthalmoscope red reflex in the presence of hyperglycemia.

Editorial: HYPOPHYSECTOMY IN DIABETES MELLITUS. Brit. M. J. *2*:779-80, September 24, 1955.

The experiences of Kinsell in America and Luft in Sweden are discussed concerning hypophysectomy in juvenile diabetes. The procedure is felt to be quite radical. It is suggested that a less dangerous procedure, such as irradiation or chemical means, may be found to inhibit pituitary activity.

Editorial: INSULIN AND THE HEART. Brit. M. J. *2*:780, September 24, 1955.

The work of Ungar and Bing in catheterizing the coronary sinus to study myocardial metabolism in diabetes is commented upon.

Editorial: VITAMIN B_{12} IN DIABETES. Orientación Méd. *4*:601, July 1, 1955.

As to the physiologic activity of vitamin B_{12}, the following hypotheses have been mentioned to define its role: 1) it is a maturation factor in erythropoiesis (extrinsic factor); 2) is a growth-promoting factor; 3) it plays a role in the synthesis of lipid complexes—hence its use in peripheral neuropathy, since nerve sheath has a large content of lipid complexes. The dosages recommended in diabetic patients affected by neurologic involvement are from 500 to 1,000 mcg. daily for a period of 1 to 2 weeks. (Spanish)

Farrell, Gordon L.; Rauschkolb, Elizabeth W.; and Royce, Paul C.: SECRETION OF ALDOSTERONE BY THE ADRENAL OF THE DOG: EFFECTS OF HYPOPHYSECTOMY AND ACTH. Am. J. Physiol. *182*:269-72, August 1955.

The rates of secretion of 17-hydroxycorticosterone, aldosterone, corticosterone, 11-desoxy-17-hydroxycorticosterone, and 11-desoxy-corticosterone by the adrenal of sham-hypophysectomized, hypophysectomized, and hypophysectomized-ACTH-treated dogs have been determined. Aldosterone was found to be the major steroid which influences electrolyte metabolism in the adrenal secretion. The rates of secretion of the steroids, with the exception of aldosterone, decreased to one-seventh to one-twelfth of control levels during the period 6 to 10 hours post-hypophysectomy. The rate of secretion of aldosterone after hypophysectomy was approximately 42 per cent of control rates. Infused ACTH induced a marked increase in the rate of secretion of 17-hydroxycorticosterone, corticosterone, 11-desoxy-17-hydroxycorticosterone, and 11-desoxycorticosterone but a relatively small increase in the rate of secretion of aldosterone.

Feller, D. D.; and Huff, Rex L.: LIPID SYNTHESIS BY ARTERIAL AND LIVER TISSUE OBTAINED FROM CHOLESTEROL-FED AND CHOLESTEROL-ALCOHOL-FED RABBITS. Am. J. Physiol. *182*:237-42, August 1955.

The authors studied conversion of acetate-2-C^{14} to

fatty acids, nonsaponifiable lipids, and carbon dioxide in slices of liver and strips of aorta obtained from normal, cholesterol-fed, and cholesterol-alcohol-fed rabbits. Serum and tissue lipid concentrations have been measured in these animals. Feeding of alcohol with cholesterol had little or no effect on elevated tissue lipid concentrations or on the induced hypercholesterolemia of cholesterol-fed rabbits. Sclerotic arterial tissue converted acetate-2-C^{14} to radioactive fatty acids, nonsaponifiable lipids, and carbon dioxide to the same extent as did normal arterial tissue. Alcohol, either fed to the rabbits along with cholesterol or added to the bath containing normal tissue, had no effect on these conversions. Liver was far more active in converting acetate carbon into lipid carbon than was aorta; however, both tissues formed comparable amounts of $C^{14}O_2$. Hepatic lipogenesis, as well as hepatic cholesterogenesis, was reduced in cholesterol-fed rabbits; no effect was noted on oxidation of acetate. These results were not altered by concomitant alcohol feeding. The relative roles played by dietary cholesterol and by endogenously synthesized cholesterol in cholesterol deposition in arterial walls have not been clarified, but it is clear that ingested cholesterol regulates hepatic but not arterial lipid synthesis.

Field, James B.: PREVENTION OF ADRENAL CORTICAL HYPERTROPHY IN DIABETIC RATS BY THE USE OF INSULIN. Endocrinology 56:499-506, May 1955.

Regulation of the diabetes in alloxanized rats with insulin during a 72-hour period prevented the adrenal hypertrophy occurring in the untreated animals. The results on a 21-day period, however, were inconclusive.

Fisher, A. M.: INSULIN PREPARATIONS. Canad. M. A. J. 73:1-8, July 1, 1955.

The composition and some of the properties of insulin preparations in use today in Canada and the United States are presented. Some other preparations of interest also received brief comment.

Fontana, Guiseppe: CONTRIBUTION TO THE PROBLEM OF DIABETIC RETINOPATHY AND INSULIN TREATMENT (EXPERIMENTAL STUDIES). Arch. ottal. 58:5-32, January-February 1954 (Abstracted in Am. J. Ophth. 38:427, September 1954).

Intercapillary glomerulosclerosis is instrumental in determining the appearance of diabetic retinopathy and in determining that insulin treatment is not harmful. Hypoglycemia, however, must be avoided and arterial hypertension kept under control, since the latter rises as the glycemia improves.

Foreign Letters: PULMONARY TUBERCULOSIS, DIABETES, AND CORTISONE. J.A.M.A. 159:212, September 17, 1955.

Although extreme caution is essential regarding the use of corticotropin and cortisone in patients with infectious diseases, especially tuberculosis, tuberculosis and most other diseases are not aggravated by these agents if a suitable chemotherapeutic agent is administered at the same time. Diabetes, even when associated with severe tuberculosis, does not constitute a formal contraindication to the use of adrenal corticosteroids.

Foreign Letters: VIRUS HEPATITIS AND DIABETES. J.A.M.A. 158:1542, August 27, 1955.

In epidemics of homologous serum jaundice, this disease was particularly common among patients with diabetes mellitus. The speakers emphasized the protracted course of hepatitis in diabetic patients, the large number of patients whose diabetes becomes worse in the course of hepatitis, and the possibility of a post-hepatitic, nephrotic attack.

Gerber, Philip; and Sindoni, Anthony, Jr.: ABSENCE OF DEGENERATIVE CHANGES 20 YEARS AFTER DIABETIC COMA WITH A BLOOD SUGAR OF 1850. Am. J. Digest. Dis. 21:331-34, November 1954.

This is a case history of a patient with diabetes mellitus of 20 years' duration who shows no degenerative vascular changes, even though the blood sugar has been very high on many occasions and the case has been complicated with infections, pregnancies, surgical procedures, and severe coma.

Goodman, Joseph I.: ETIOLOGY OF THE DIABETIC NEUROPATHIES. Am. J. Digest. Dis. 22:236-39, August 1955.

The etiology of diabetic neuropathy is discussed from the standpoint of 3 possible causative factors: atherosclerosis, vitamin deficiency, and diabetes.

The author did not feel that ischemia of the nerves due to atherosclerosis was the etiological factor.

The roll of vitamins (especially vitamin B) in carbohydrate metabolism and their possible etiology in diabetic neuropathy is discussed, with the conclusion that thiamin deficiency is not the true etiological factor and that treatment with vitamins does not suffice to bring relief in true diabetic neuropathy.

The author agrees that the etiology is unknown but that good control of the diabetes is still the best treatment which we have. He believes that the cause lies in some obscure metabolic change in nerve tissue coincidental to uncontrolled diabetes.

Gravano, Luis: DIABETIC COMA FOLLOWING AN ALLERGIC REACTION TO INSULIN TREATED WITH ACTH. Día méd. 27:1859-70, August 22, 1955.

A 48-year-old female diabetic showed a severe urticaria following the administration of PZI. Twenty-five milligrams of ACTH diluted in 500 cc. of normal saline were given intravenously during a period of 2 hours. The urticaria reaction improved dramatically; but during the next 48 hours, a picture of increasing acidosis developed until the patient became comatose. The treatment in this case required 1,250 units of insulin during the first 24 hours. After proper therapy of the diabetic coma, the patient improved and was discharged. (Spanish)

Gurling, K. J.: EVALUATION OF AN ANDROGEN, METHYLANDROSTENEDIOL, IN THE TREATMENT OF DIABETIC RETINOPATHY. Brit. J. Ophth. *39*:151-54, March 1955 (Abstracted in Am. J. Ophth. *40*:302, August 1955).

Gurling reports his observation of 27 patients in various stages of diabetic retinopathy treated with methylandrostenediol. In no case was the diabetic retinopathy appreciably altered.

Hausberger, Franz X.; and Ramsay, Andrew J.: STEROID DIABETES IN GUINEA PIGS: EFFECTS OF HYDROCORTISONE ADMINISTRATION ON BLOOD AND URINARY GLUCOSE, NITROGEN EXCRETION, FAT DEPOSITION, AND THE ISLETS OF LANGERHANS. Endocrinology *56*:533-40, May 1955.

Male guinea pigs developed steroid diabetes following subcutaneous injections of hydrocortisone. The islets of the pancreas showed marked hypertrophy, new beta-cell formation and degranulation. Prolonged administration led to severe hydropic degeneration. The most effective dosage of hydrocortisone was 5 mg. given twice daily.

Headstream, James W.; and Wortham, James T.: BILATERAL TOTAL ADRENALECTOMY IN DIABETICS WITH DEGENERATIVE VASCULAR DISEASE. J. Urol. *74*:1-7, July 1955.

The authors report a small series of diabetics with degenerative vascular disease in which bilateral adrenalectomy was performed. The results tend to confirm the attitude that vascular deterioration of the type seen in diabetics may involve abnormal adrenal cortical function. It appears that if adrenalectomy is to be successful, it should be done relatively early in the arteriolar degenerative processes; and the results suggest that in well-selected patients, it may prove practical and hopeful therapy. (See their paper Diabetes *3*:5, 367-74, 1954.)

Houssay, B. A.; Anderson, E.; Bates, R. W.; and Li, Choh Hao: DIABETOGENIC ACTION OF PROLACTIN. Endocrinology *57*:55-63, July 1955.

Three different preparations of prolactin were injected into dogs and cats. Those with an intact pancreas did not show hyperglycemia, but those with a surgically reduced pancreas developed transitory diabetes. Though the diabetogenic activity of prolactin was greater than that of ACTH, it was less than that of somatotropin. The thyroid and adenohypophysis are not required for the prolactin diabetogenic effect.

There was no detectable somatotropin in the prolactin preparations used. The preparations revealed a small amount of ACTH.

Inderbitzen, T.; and Meyer, H.: ON INSULIN-RESISTANCE. Schweiz. med. Wchnschr. *85*:501-02, May 21, 1955.

The cause of insulin resistance in a case of diabetes mellitus was true antibody formation. Not insulin per se but nonspecific protein bodies are probably the antigen responsible for the antibody formation.

The patient was desensitized against NPH Insulin Lilly. Local reaction at the site of injections was prevented by addition of an antihistaminic substance to the insulin. (German)

Ingle, Dwight J.; Morley, Erving H.; and Stetten, DeWitt, Jr.: METABOLISM OF GLUCOSE IN RESTING AND WORKING RATS. Am. J. Physiol. *182*:263-66, August 1955.

Different loads of C^{14}-glucose were administered by continuous intravenous infusion into anesthetized rats over a period of 12 hours. Glycosuria was induced in all of the animals. Nonworking rats were compared with rats subjected to faradic stimulation of either one or both hind legs. The urinary excretion and the hepatic storage of isotopic glucose were suppressed by muscle work—to the greatest extent when both legs were working. Muscle work caused a marked increase in the oxidation of isotopic glucose, an accompanying rise in the expiration of nonisotopic CO_2, and a decrease in respiratory quotient.

Innerfield, Irving: INTRAMUSCULAR TRYPSIN-IN-OIL IN ACUTE THROMBOPHLEBITIS, DIABETIC CELLULITIS, AND LEG ULCER. Surgery *36*:1090-1101, December 1954.

Ninety patients with acute thrombophlebitis, diabetic cellulitis, and leg ulcer were treated with an intramuscular trypsin-in-oil preparation. It was noted that there was a reduction in the acute inflammation. In comparing it with an anticoagulant in the treatment of thrombophlebitis, the author felt trypsin to be safer, more effective, and more economical.

Joshi, Ram A.; and Probstein, J. G.: BENIGN CYSTIC ISLET-CELL TUMOR OF THE HEAD OF THE PANCREAS. REPORT OF A CASE PROBABLY OF DELTA-CELL ORIGIN.

A.M.A. Arch. Surg. *71*:74-77, July 1955.

The authors report a case of cystic islet-cell adenoma of the head of the pancreas, probably originating from delta cells. They state that they could find a report of only one other tumor arising from this cell type in the literature.

Kelemen, George: AURAL CHANGES IN THE EMBRYO OF A DIABETIC MOTHER. A.M.A. Arch. Otolaryng. *62*: 357-69, October 1955.

The author describes a 26-year-old diabetic who underwent abdominal hysterotomy in the sixth month of pregnancy because of rapidly progressing retinopathy. Her diabetes was of 15 years' duration at that time. Pathologic examination of the embryo revealed hemorrhagic changes in the structures of the middle and inner ear which were unique. The significance of these changes is discussed and has led the author to suggest that closer study be made of the hearing organ in the progeny of diabetic mothers.

Kenny, A. J.: EXTRACTABLE GLUCAGON OF THE HUMAN PANCREAS. J. Clin. Endocrinol. *15*:1089-1105, September 1955.

Thirty-five human pancreases, obtained at autopsy, were assayed for extractable glucagon (hyperglycemic-glycogenolytic factor). Extracts of the pancreases were compared with a standard, partially pure preparation of glucagon in a series of multiple-dose assays, by use of surviving rabbit liver slices as the assay system. The presence of glucagon in the human pancreas was confirmed. There was a large variation among the values of the relative potencies of the pancreatic extracts assayed. Pancreases from females appeared to contain significantly more glucagon than those of males. There was a tendency for extractable-glucagon levels to fall with increasing age, but this correlation was significant only among the females. No significant differences were found between 19 diabetics and 12 nondiabetics, nor between various categories within the diabetic group. Although not excluding such a relationship, the results provide no support for the view that glucagon is a major factor in the pathogenesis of diabetes mellitus.

Kinoshita, Jin H.: CARBOHYDRATE METABOLISM OF LENS. A.M.A. Arch. Ophth. *54*:360-68, September 1955.

The metabolism of glucose in lens proceeds mainly by the glycolytic mechanism. However, the aerobic phase of glucose metabolism in lens is different from that of other tissues. The production of carbon dioxide from glucose is largely effected through the direct oxidative pathway, with little participation by the citric acid cycle. The possibility of an alternate mechanism for the reoxidation of reduced TPN is presented.

Langdon, Robert G.; and Weakley, David R.: THE INFLUENCE OF HORMONAL FACTORS AND OF DIET UPON HEPATIC GLUCOSE-6-PHOSPHATASE ACTIVITY. Bull. Johns Hopkins Hosp. *97*:180-81, August 1955.

The hepatic utilization of glucose is impaired in alloxan diabetes. It may be that hexokinase is less active in the diabetic animal than in the normal animal, and thus impairment in conversion of glucose-6-phosphatase is caused. Swanson and deDuve *et al.* have demonstrated the presence in the liver of a specific glucose-6-phosphatase which contributes free glucose to the blood from liver glycogen pools and other precursors of glucose-6-phosphatase. The net rate of formation of glucose-6-phosphatase depends upon the relative activity of these two enzymes. An increased activity of hepatic glucose-6-phosphatase could cause decreased utilization of glucose by the diabetic liver, even in the presence of a normal hexokinase reaction. The investigators have studied the hepatic glucose-6-phosphatase activity in normal and alloxan-diabetic rats. Their findings demonstrate that the activity of the enzyme is greatly increased in the diabetic animal. The administration of insulin restores the enzymatic activity of the diabetic animals to near normal levels. The increased activity of the enzymes seems related specifically to the diabetic state, since fasting and the administration to normal animals of pituitary growth hormone, cortisone, and adrenal cortical extract had little or no effect upon the enzyme.

Levin, M. B.: VITAMIN B_{12} IN NEURO-METABOLISM (PRELIMINARY CLINICAL REPORT). Am. J. Digest. Dis. *22*:96-97, April 1955.

Massive doses of B_{12} were given to patients with varying neurological disorders with excellent results. Between 5,000 and 10,000 mcg. injected intramuscularly 2 to 3 times weekly was necessary for effective dosage in many cases. It was felt that, if they were not beyond a certain stage, some neurological conditions hitherto considered irreversible may be reversible with full vitamin B_{12} dosage.

Lossow, W. J., and Chaikoff, I. L.: CARBOHYDRATE SPARING OF FATTY ACID OXIDATION. I. THE RELATION OF FATTY ACID CHAIN LENGTH TO THE DEGREE OF SPARING. II. THE MECHANISM BY WHICH CARBOHYDRATE SPARES THE OXIDATION OF PALMITIC ACID. Arch. Biochem. *57*:23-40, July 1955.

The authors have investigated the carbohydrate sparing of fatty acid oxidation in rats. This action is greater in fed animals and is more pronounced in the case of the larger-chain fatty acids. Carbohydrate does not spare the oxidation of acetate. The sparing of the oxidation of palmitic acid results principally from restriction of its breakdown. It is suggested that the degree of sparing

of oxidation of fatty acids of chains of less than 16 carbons is related to the capacity of conversion of a particular fatty acid directly to 16 and 18-carbon fatty acids.

Martinez, Carlos: EFFECT OF BARBITURIC ACID ON ALLOXAN DIABETES IN RATS AND DOGS. Am. J. Physiol. *182*:267-68, August 1955.

The diabetogenic effect of alloxan in rats and dogs is counteracted by pretreatment with barbituric acid, given either intraperitoneally or intravenously. Barbituric acid does not protect against diabetes when it is given following the injection of alloxan.

Mellinkoff, Sherman M.; Boyle, David; Frankland, Marjorie; Greipel, Margaret: THE EFFECT OF AMINO ACID ADMINISTRATION UPON THE BLOOD SUGAR CONCENTRATION. Stanford M. Bull. *13*:117-24, May 1955.

The infusion of 250 cc. of 10 per cent amino acids in 45 minutes was followed by a significant drop in the blood sugar level. A similar fall was noted after ingestion of the solution. The authors postulate that the blood amino acids may have stimulated the secretion of insulin.

Miratynska-Rusinowa, E.; and Lisiecka-Adamska, H.: LENTICULAR CHANGES IN DIABETIC PATIENTS. Klinika Oczna *24*:165-73, 1954 (Abstracted in Am. J. Ophth. *40*:300, August 1955).

Lenticular changes in diabetics appear in two forms: refractive changes and opacities. Refractive errors were found most commonly in untreated or poorly treated diabetics and most often after the fortieth year of life. Only 1.7 per cent of diabetics had characteristic diabetic opacities.

Miratynska-Rusinowa, E.; and Lisiecka-Adamska, H.: OCULAR SYMPTOMS IN DIABETICS. Klinika Oczna *24*: 75-76, 1954 (Abstracted in Am. J. Ophth. *38*:450, September 1954).

The authors summarize the results of examination of 667 diabetic patients. Disease of the iris was seen in 4. In 129 patients (19 per cent), diabetic retinitis was found. There were aneurysms in 195 (27 per cent) and arteriosclerotic changes in 205 patients (30 per cent). Four cases of optic neuritis could be attributed to diabetes.

Mirsky, I. Arthur; Perisutti, Gladys; Jinks, Robert: THE DESTRUCTION OF INSULIN BY INTACT MICE. Endocrinology *56*:484-88, April 1955.

The intact mouse appeared to destroy I^{131}-labeled exogenous insulin at a relatively rapid rate. This reaction is thought to be the result of insulinase activity.

Moorhouse, J. A.; and Kark, R. M.: CORRECTION OF METABOLIC ABNORMALITIES IN DIABETES MELLITUS BY CONTINUOUS FRUCTOSE FEEDING. Clin. Res. Proc. *3*:203-04, November 1955.

Continued 24-hour feedings of a diet in which fructose was the only carbohydrate used was studied in an attempt to learn whether this would restore liver glycogen, inhibit glycogenolysis, and lower blood sugar. A synthetic liquid diet was given by intragastric tube and feeding pump for several days or weeks. Either glucose or fructose constituted the only carbohydrate. All other elements in the diet were constant. In 3 of 4 diabetic patients, there was a well-defined fall in blood and urine levels of glucose and acetone during fructose feedings and diminished urinary excretion of potassium, phosphate, and nitrogen. An acromegalic patient with insulin-resistant diabetes showed no change in glucose levels, but blood acetone fell markedly.

Murray, John F.; and Tinsley, Clarence M.: ISLET CELL ADENOMA OF THE PANCREAS: REPORT OF A CASE FOLLOWED FOR EIGHT YEARS, WITH AUTOPSY FINDINGS. Stanford M. Bull. *13*:80-83, May 1955.

A case is presented of islet cell adenoma followed for eight years before coming to autopsy. Hypoglycemia and loss of consciousness were readily controlled by dietary measures, so surgery was deferred. Patient became obese. Death was thought to be unrelated to the functioning islet cell adenoma.

Nastri, F.; and D'Ermo, F.: PROTEIN CONTENT OF THE BLOOD OF DIABETICS WITH RETINOPATHY. Boll. ocul. *33*:3-10, January 1954 (Abstracted in Am. J. Ophth. *38*:283, August 1954).

In diabetes with retinopathy, the reduction of blood proteins and the increase in beta and gamma globulin is more marked if the disease is complicated by renal and hepatic affection. The chemical alterations may predispose to the ocular lesions.

Nonnenmacher, H.: DIABETES MELLITUS, DIABETIC RETINOPATHY AND HYPERTENSION IN THE POSTWAR PERIOD. Klin. Monatsbl. Augenh. *124*:579-83, 1954 (Abstracted in Am. J. Ophth. *38*:450, September 1954).

Diabetic retinopathy and diabetes with high blood pressure have become more frequent during the last years than in the years immediately following World War II. The statistics are from a municipal hospital near Dresden. In 1947, only 1 out of 6 diabetic patients had hypertension. In 1952, every other hospitalized patient with diabetes also had a vascular hypertension. This association is more frequent in women. In these cases, the management of the hypertension is of utmost importance.

Peel, J. H.: MANAGEMENT OF THE PREGNANT DIABETIC. Brit. M. J. 2:870-74, October 8, 1955.

The management of the pregnant diabetic is discussed. It is felt that stilbesterol and ethisterone have no effect on fetal survival.

Peifer, J. J.; and Holman, Ralph T.: ESSENTIAL FATTY ACIDS, DIABETES, AND CHOLESTEROL. Arch. Biochem. 57:520-21, August 1955.

The authors suggest that atherosclerosis may be related to essential fatty acid deficiency or its faulty metabolism. Cholesterol may intensify essential fatty acid deficiency and consequently be involved in this manner in the production of atherosclerosis.

Pennoyer, Miriam M.; and Hartmann, Alexis F.: MANAGEMENT OF INFANTS BORN OF DIABETIC MOTHERS. Postgrad. Med. *18*:199-206, September 1955.

The authors present in detail a program for the handling of infants born of diabetic mothers in the neonatal period, together with some comment on the management of diabetes during pregnancy and the behavior of the blood sugar of infants born of diabetic mothers in the neonatal period.

Persky, Murry; Linsk, Joseph; Isaacs, Marian; Jenkins, John P.; Rosenbluth, Milton; and Kupperman, Herbert S.: ACUTE EFFECTS OF INTRAVENOUS HYDROCORTISONE ON GLUCOSE AND INSULIN TOLERANCES, AND LEVELS OF SERUM AND URINARY INORGANIC PHOSPHORUS. J. Clin. Endocrinol. *15*:1247-56, October 1955.

The acute effects of intravenous 17-hydrocorticosterone (hydrocortisone) on glucose tolerance, insulin tolerance, and the level of inorganic serum phosphorus were studied. Infusions of hydrocortisone alone (hydrocortisone-tolerance test), hydrocortisone with oral glucose (hydrocortisone-glucose-tolerance test), and hydrocortisone with intravenous insulin (hydrocortisone-insulin-tolerance test) were administered. During hydrocortisone infusion alone, no hyperglycemic effect was noted, whereas there was a consistent decrease in glucose tolerance during the hydrocortisone-glucose-tolerance test. In spite of the decreased glucose tolerance, no anti-insulin effect could be demonstrated. Profound decreases in the level of serum phosphorus were observed during the hydrocortisone-glucose-tolerance tests. Eosinophil falls indicated that active physiologic effects were achieved. Postulated mechanisms for the changes in glucose metabolism are (1) increased gluconeogenesis, (2) increased peripheral glucose utilization, (3) secretion of a hyperglycemic-glycogenolytic factor from the alpha cells of the pancreas, and (4) inhibition of reflex secretion of insulin under induced alimentary hyperglycemia.

Petersen, Villy Posborg; and Lotspeich, William D.: FURTHER ASPECTS OF THE ENDOCRINE REGULATION OF KETOGENESIS. Am. J. Physiol. *182*:273-78, August 1955.

The authors report upon the interrelations between anterior pituitary growth hormone and the adrenal cortex in the production of ketosis in the female rat. Measurements were made of acetoacetate formation by excised liver slices, of liver glycogen, and of total blood ketones in intact and in adrenalectomized preparations after administration of growth hormone (GH) products of varied purity, of thyroid-stimulating (TSH) hormone, and of cortisone.

It was observed that (a) TSH is intensely ketogenic and probably the factor responsible for the ketogenic effects of certain "purified" GH preparations, (b) the adrenalectomized rat is capable of acetoacetate synthesis but does not respond to hormonal stimulation, and (c) liver glycogen content and ketone production are not always directly related.

Plattner, H. C.; and Dufour, J. J.: UNUSUAL METABOLIC DISORDERS IN A TUBERCULOUS DIABETIC FEMALE SHOWING A SEVERE MALNUTRITION (HYPOCHLOREMIC, HYPOKALEMIC ALKALOSIS WITH KETOSIS). Presse méd. 63:829-31, May 28, 1955.

A female patient with pulmonary tuberculosis and diabetes was found to have glycosuria and a hyperglycemia of 4 gm. per liter. Her urine showed a high content of acetone; yet the alkaline reserve of this patient was, paradoxically, elevated. The electrolyte imbalance is regarded as a part of the malnutrition syndrome. A proper correction of this electrolyte imbalance resulted in the patient's improvement and made possible the effectiveness of the therapy for tuberculosis. (French)

Queries and Minor Notes: ABDOMINAL SYMPTOMS IN DIABETES. J.A.M.A. *159*:233-34, September 17, 1955.

In diabetic patients, the latency of symptoms and signs of abdominal infections, particularly in the appendix and gallbladder, is notorious. It repeatedly happens that an appendix or a gallbladder explodes in the ward while the patient is under observation for an entirely unrelated disorder. In diabetic coma, abdominal symptoms are so common that, in a considerable percentage of the cases, a surgical consultation is almost routine; and if there is doubt, exploration of the abdomen is carried out. A pseudoperitonitis was recognized as long ago as in Kussmaul's original description of coma. The abdominal distress, facies hippocratica, the tense abdomen, and the leukocytosis conformed closely to appendicitis; but, in Borning's case, the symptoms recurred in several subsequent bouts of coma, although the appendix had been removed several years before.

Queries and Minor Notes: SACCHARIN AND THROMBOCYTOPENIC PURPURA. J.A.M.A. *159*:93, September 3, 1955.

There is no evidence that saccharin is in any way related to the development of thrombocytopenic purpura.

Queries and Minor Notes: STARVATION TREATMENT FOR DIABETES. J.A.M.A. *159*:92-93, September 3, 1955.

Undernutrition is acknowledged universally to have merit in the treatment of the obese diabetic patient; in most diabetics, it will often result in the urine becoming sugar-free and may make unnecessary the use of insulin. Undernutrition explained why certain bizarre diets or diets with high fat and low carbohydrate and protein were of value. Actually, they were undernutrition diets. Even today, utilization of the principle of undernutrition, combined with insulin, gives the speediest and best results in the inauguration of treatment.

Reinecke, Roger M.: RENAL ARTERIOVENOUS CHANGES IN LACTIC ACID AND SUGAR IN THE EVISCERATED RAT. Am. J. Physiol. *182*:243-46, August 1955.

The renal arteriovenous increase in blood sugar which has been observed in the eviscerated rat with ligated ureters is accompanied in some instances by a concurrent renal arteriovenous decrease in lactic acid. In some instances, the renal arteriovenous increase in sugar is larger than the decrease in lactic acid.

Schemm, F. R.; Gilson, Betty; Hurst, W. W.; Gilson, John S.; Camara, A. A.; and Layne, John A: HYPOTONIC INTRAVENOUS SOLUTIONS — THEIR EFFECT ON THE BLOOD AND THEIR CLINICAL USEFULNESS. Rocky Mountain M. J. *52*:791-800, September 1955.

Clinical evaluation of the use of intravenous hypotonic (half-isotonic) saline or dextrose infusion, particularly for patients who require large amounts of fluid replacement without electrolyte replacement or overburdening, is discussed. Well-controlled clinical experiments, measuring blood volume, rate of urine formation, and amount of sodium excretion during and after infusion and, of course, serum values of plasma electrolytes, were performed on patients on the general medical wards who were in the hospital either for diagnostic studies or very minor illnesses. The patients utilized were all in a state of "normal hydration." The following conclusions were reached: (1) The intravenous use of these hypotonic solutions produced no ill effect. (2) No intravascular hemolysis of erythrocytes was shown to occur. (3) There was no significant dilution of plasma electrolytes. (4) There was no significant lowering of plasma osmotic pressure or plasma specific gravity, even in acute experiments involving rapid intravenous infusions of hypotonic solutions.

Seltzer, Holbrooke S.; Fajans, Stefan S.; and Conn, Jerome W.: SPONTANEOUS HYPOGLYCEMIA AS A MANIFESTATION OF EARLY DIABETES MELLITUS. Clin. Res. Proc. *3*:203, November 1955.

A large number of patients with early mild diabetes suffer from spontaneous hypoglycemia. Symptoms of hypoglycemia represented the chief complaint in 54 per cent of 87 patients. The hypoglycemia is stimulative, occurring 3 to 5 hours postprandial. The blood sugar levels at the third to the fifth hour range from 25 to 50 mg. per 100 cc. Forty-one had a positive family history of diabetes. Twenty-four showed a combination of symptomatic hypoglycemia and family history of diabetes. The fasting blood sugar exceeded 110 mg. per 100 cc. in only one patient.

Serfaty, Salomón Oscar: BLOOD SUGAR LEVELS IN PREGNANCY. Prensa méd. argent. *42*:964-72, April 8, 1955.

In a series of 166 pregnant women, the determination of blood sugar levels varied from 45 mg. per 100 cc., the lowest value, up to 113 the highest value. In dividing the series into two groups as to the duration of pregnancy, the average blood sugar value for the first group was 77 mg. per 100 cc.; for the second group, 74 mg. per 100 cc. It is confirmed that the renal threshold for glucose is decreased in pregnancy and also that hypoglycemia is frequently seen in pregnant women. (Spanish)

Skilman, Thomas B.; Kessler, Margaret F.; and Knowles, Harvey C., Jr.: OBSERVATIONS ON THE USE OF 10 PER CENT GLUCOSE IN THE EARLY TREATMENT OF DIABETIC ACIDOSIS. Clin. Res. Proc. 3:203, November 1955.

Series are reported of the use of excessive glucose in the treatment of diabetic acidosis in 128 consecutive cases presenting clinical and laboratory evidence of ketoacidosis. Fifty-one received 10 per cent glucose during the first 6 hours. The remaining 77 received no glucose or 5 per cent glucose from onset. Other details of management were similar in both groups. It was concluded that the administration of 10 per cent glucose at onset of treatment resulted in continuation of hyperglycemia, sustained polyuria, and diminished positive water balance. The period of ketonuria was shortened in the 10 per cent glucose group, but no significant difference in mortality was noted.

Teng, Ching Tseng: STUDIES ON CARBOHYDRATE METABOLISM IN RAT KIDNEY SLICES. III. EFFECT OF ADRENALECTOMY AND HYPOPHYSECTOMY ON GLUCOSE UPTAKE AND GLUCOSE FORMATION. Arch. Biochem. *57*:61-65, July 1955.

The author has studied the uptake and formation of glucose by kidney slices from adrenalectomized and

hypophysectomized rats. In the former animals, there was a reduction of formation without change in uptake. In the latter animals, there was an increase in uptake with no change in formation.

Teng, Ching Tseng: STUDIES ON CARBOHYDRATE METABOLISM IN RAT KIDNEY SLICES. IV. EFFECT OF CATIONS ON METABOLISM OF GLUCOSE, PYRUVATE AND GLYCEROL. Arch. Biochem. 57:66-70, July 1955.

Studies were conducted on the metabolism of glucose, pyruvate, and glycerol by rat kidney slices in three media containing varying concentrations of potassium, sodium, magnesium, and calcium. Rates of uptake of all three substrates and the rates of glucose and lactate formation were greater in high-sodium media than in high-potassium media. Variations of magnesium and calcium ion concentrations had no effect.

Thiers, H.: BIOLOGICAL AND THERAPEUTICAL INTEREST OF STIGMASTEROL. Presse méd. 63:820-21, May 28, 1955.

Stigmasterol is a new liposoluble vitamin. It is a sterol of plant origin and can be converted into stigmacalciferol, which has a vitamin D activity. That compound is described as the antistiffness factor essential for guinea pigs. In man, therapeutic experience showed it to have the effectiveness of vitamin D; in fact, a clinical picture of vitamin D intoxication can be induced by the use of this drug. The author mentioned as indications for its use scleroderma, postphlebitic inflammatory cellulitis, certain neuralgias and certain muscular rheumatisms, rhizomelic spondylosis, and, more questionably, polyarthritis. (French)

Tombleson, S. B.: DIABETES MELLITUS AND FERTILITY. New Zealand M. J. 295:230-32, June 1954 (Abstracted in Am. J. Digest. Dis. 22:24, January 1955).

A study of 243 men and women reveals no evidence of loss of fertility in women but a slight reduction in diabetic men. The authors found that fetal loss was high, although not because of abortion.

Valls Rovira, A.: ISCHEMIC ULCERS IN DIABETICS. Ulceras de las piernas de origen neurovascular, pp. 85-87, chapter 13, 1950. (Book compiled by F. Martorell)

The diagnosis of ischemic ulcers in diabetics is based on (1) the presence of a painful ulcer located in the toes, which is rarely seen in the supramalleolar region; (2) signs of arteriosclerosis obliterans and loss of peripheral pulses in the affected site; (3) presence of metabolic disturbances (glycosuria and hyperglycemia); (4) commonly associated bone alterations, such as osteomyelitis and osteoarthritis.

If the ulcer and its borders are painless and it is located in the plantar surface, then it should be classified as a neurotropic ulcer.

The treatment of ischemic ulcers includes hospitalization, correction of the metabolic disturbance, treatment or prophylaxis of secondary infection with the proper antibiotic, and débridement of the necrotic tissue. Lumbar sympathectomy is sometimes indicated. (Spanish)

Vargas, L.; and Silva, L.: ON THE PROBLEM OF THE ABSORPTION OF PROTAMINE-ZINC-INSULIN IMPLANTED SUBCUTANEOUSLY. PRESENCE OF BLOOD VESSELS IN THE CAPSULE. Acta physiol. latinoam. 5:10-21, 1955.

The absorption of protamine zinc insulin-cholesterol pellets implanted subcutaneously has been corroborated by (a) decrease in weight of the pellets with a daily diminution rate of approximately 1 per cent; (b) fatal hypoglycemia when the implanted dose is toxic (over 150 units per kg.); (c) control of the diabetic state of human patients by subcutaneous implantation of PZI-cholesterol. Histologic examination of 80 specimens from the site of implantation of PZI, PZI-cholesterol, and cholesterol definitely demonstrate the presence of blood vessels in the capsule formed around these substances. The control of hyperglycemia in the diabetic patients lasted for a period of 20 to 81 days without the help of insulin injections. The series included 11 diabetic patients whose insulin requirements varied from 50 to 80 units of PZI daily. (Spanish)

Vignale, Bartolomé; and Montero, Eustaquio D.: IDIOPATHIC HYPERLIPEMIA WITH XANTHOMATOUS LESIONS, MILD DIABETES, AND SPLENOMEGALY. An. Fac. med. Montevideo 39:409-14, September-December 1954.

A case of eruptive xanthoma in idiopathic hyperlipemia developing in an adult with mild diabetes and splenomegaly is presented. The diabetes was perfectly controlled by diet without insulin. A diet low in cholesterol led to the disappearance of the xanthomatous lesions in about three weeks and diminution of the blood cholesterol to the normal value, as well as disappearance of hyperlipemia. (Spanish)

Weinstock, I. M.; Shoichet, I.; Goldrich, A. D.; and Milhorat, A. T.: THE EFFECT OF VITAMIN E DEFICIENCY ON THE OXIDATION OF TRICARBOXYLIC ACID CYCLE INTERMEDIATES. Arch. Biochem. 57:496-505, August 1955.

The authors have found that the oxidation of five of six added tricarboxylic acid substrates by washed liver homogenates from vitamin E-deficient rabbits was 60 to 600 per cent higher than controls when supplemented with ATP. Fluoride did not reduce oxidation to control levels. Replacing ATP with ADP or AMP eliminated the difference in oxygen consumption.

Welsh, George W.; Henley, Elaine D.; Williams, Robert H.; and Elgee, Neil J.: METABOLIC STUDIES OF I^{131}-LABELED INSULIN IN NORMALS AND DIABETICS. Clin. Res. Proc. 3:122, April 1955.

Tracer amounts of labeled insulin were given intravenously to 15 nondiabetic controls and 40 diabetics. All controls showed rapidly decreasing concentrations of plasma-precipitable radioactivity from the initial theoretic 100 per cent to an average of 20 per cent of dose in 15 minutes and 7.5 per cent in 60 minutes. Diabetics maintained markedly higher levels up to 80 per cent in 60 minutes.

Since, in diabetics, plasma concentrations of labeled insulin remain high and degradation is less, there appear to be specific factors which interfere with the dispersion, degradation, and utilization of insulin by cells. These studies suggest that the factors are extracellular.

Whitney, John E.; and Roberts, Sidney: INFLUENCE OF PREVIOUS DIET ON HEPATIC GLYCOGENESIS AND LIPOGENESIS. Am. J. Physiol. *181*:446-50, May 1955.

Studies have been carried out on the influence of diets high in carbohydrate or fat and subsequent fasting on hepatic synthesis of carbohydrate, fatty acids, and cholesterol in the rat. Feeding a high-fat diet for two to three months depressed the incorporation in vitro of the methyl carbon of acetate into liver glycogen and fatty acids in fed animals. In contrast, the incorporation of isotope into hepatic cholesterol was stimulated in fasted rats previously fed a high-fat diet. Evidence is presented which suggests that these phenomena are reflections of depressed glycogenesis, fatty acid synthesis, and accentuated cholesterogenesis in the livers of the fat-adapted animals. These adaptations appear to be established by prolonged fat feeding and tend to persist during the early fasting period.

Wilson, F. H. H.: PREGNANCY WITH DIABETES—THE PHYSICIAN'S VIEWPOINT. M. J. Australia 2:87-88, July 17, 1954. (Abstracted in Am. J. Digest. Dis. *22*:23, January 1955).

The author presents the important factors in handling a pregnancy with diabetes, such as special care for the pregnancy and very careful control of the diabetes. These are carefully described in detail, discussing the pregnancy, the fetus, the baby, the factors for a cesarean section, and a change in the insulin requirements. There is a question of the importance of pregnancy hormones as compared with the value of good diabetic management.

Wolbach, Robert A.: RENAL REGULATION OF ACID-BASE BALANCE IN THE CHICKEN. Am. J. Physiol. *181*:149-56, April 1955.

The author reports experiments in the chicken, in which administration of acids and buffers indicated that similar renal mechanisms were utilized in the chicken as in man and in the dog to compensate for the dual stresses of dietary acid ash and metabolic production of uric acid.

Wolff, O. H.; and Maddison, T. G.: INSULIN ZINC SUSPENSION IN CHILDHOOD DIABETES. Brit. M. J. 2: 413-15, Aug. 13, 1955.

The authors administered Lente insulin zinc suspension (a 3/7 mixture of amorphous to crystalline insulin zinc suspension) to 18 to 20 children with good results.

Yamagata, Shoichi; Satô, Yukio; and Nishiyama, Shoji: STUDIES ON BLOOD GLYCOGEN: BLOOD GLYCOGEN CONTENT IN DIABETES MELLITUS AND ALLOXAN DIABETES. Tohoku J. Exper. Med. *61*:7-13, Dec. 25, 1954.

A part of glycogen in the liver pours into the blood as such when the capacity of the liver to keep glycogen is diminished. This is the reason why the content of blood glycogen is elevated in the case of diabetes mellitus—the capacity of the diabetic tissues to keep sugar is reduced, owing to the diminished secretion of insulin.

The results obtained from these experiments show that the elevated content of blood glycogen of alloxan-diabetic rabbits agrees with that of diabetes mellitus patients when the capacity of the liver to keep glycogen is reduced; on the contrary, the decreased content of blood glycogen of rabbits with an acute form of alloxan diabetes suggests the diminished glycogen content of the liver.

Ziegler, Dewey K.: MINOR NEUROLOGIC SIGNS AND SYMPTOMS FOLLOWING INSULIN COMA THERAPY. J. Nerv. & Ment. Dis. *120*:75-78, July-August 1954.

Twenty-two patients were studied for this report. They were examined neurologically before and after the insulin coma therapy, and 2 more were examined only after therapy. The results of these examinations are given in detail in the article. As a result of the observations, the author suggests that a prolonged or repeated hypoglycemia is the factor associated with the sensory disorders which were noted. There is evidently a relationship between the blood sugar and the nerve function. One speculation is that the abrupt and profound fluctuations in blood sugar are possibly associated with the neuropathy often seen in diabetes.

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Preliminary Program of the 16th Annual Meeting of the American Diabetes Association

June 9-10, The Drake, Chicago, Illinois

William C. Stadie, M.D., Professor of Research Medicine, The John Herr Musser Department of Research Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, will deliver the Banting Memorial Lecture of the American Diabetes Association at its Sixteenth Annual Meeting. His address, entitled "Recent Advances in Insulin Research," will be delivered at 10:30 a.m. during the Scientific Session scheduled for Saturday morning, June 9. Dr. Stadie, who is the new editor of DIABETES, will be presented with the Banting Medal at the Annual Banquet of the Association to be held that evening.

The program of the Sixteenth Annual Meeting follows, including pertinent information about the Scientific Sessions. It is important to note that the first Scientific Session will be held *Saturday morning instead of Saturday afternoon as has been customary,* and that *there will be no Joint Meeting this year with The Endocrine Society.*

Registration:
Friday, June 8: 8:30 a.m.-7:00 p.m.
Saturday, June 9: 8:30 a.m.-5:30 p.m.
Sunday, June 10: 8:30 a.m.-5:30 p.m.

Social Hour: Saturday, June 9, 6:30 p.m.

Banquet: Saturday, June 9, 7:30 p.m.

Annual Business Meeting: Sunday, June 10, 2:00 p.m.

Groups scheduled to convene before the Annual Meeting include: Committees, June 6 and 7; Council, June 8; Board of Governors, June 8-9; Assembly of Delegates, June 9.

SCIENTIFIC SESSION

Saturday, June 9, 9:00 a.m.

HENRY T. RICKETTS, Presiding

Preliminary Observations of the Effect of Amphenone in Diabetes

JOSEPH J. HOET (by invitation), ALBERT E. RENOLD, GEORGE W. THORN and ROY HERTZ (by invitation), Harvard Medical School and Peter Bent Brigham Hospital, Boston, Mass., and the National Cancer Institute of the National Institutes of Health, Washington, D. C.

Steroid Diabetes in the Cat

JOHN BUSE (by invitation), KARE GUNDERSEN and FRANCIS D. W. LUKENS, George S. Cox Medical Research Institute, University of Pennsylvania School of Medicine, Philadelphia, Pa.

Changes in the Serum Proteins and Polysaccharides in Rats with Long-Term, Uncontrolled Diabetes

ELIZABETH F. TULLER (by invitation), NANCY NICHOLS, PIERRE MOINAT (by invitation), and ALEXANDER MARBLE, Baker Clinic Research Laboratory and Harvard Medical School, Boston, Mass.

Inhibition of Insulin Action by Serum Gamma Globulin

ARTHUR R. COLWELL, Northwestern University Medical School, Chicago, Ill., and ROBERT W. WEIGER (by invitation), Passavant Memorial Hospital, Chicago, Ill.

BANTING MEMORIAL LECTURE

Recent Advances in Insulin Research

WILLIAM C. STADIE, Professor of Research Medicine, The John Herr Musser Department of Research Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pa.

Relative Diabetogenicity of Prednisone, Prednisolone, and Cortisone in Human Beings: The Effect of Heredity on Response to Gluco-Corticoids

KELLY M. WEST, University of Oklahoma School of Medicine and Veterans Administration Hospital, Oklahoma City, Okla.

BANQUET

Saturday, June 9, 7:30 p.m.

Address by HENRY T. RICKETTS, President

Presentation of the Banting Medal to WILLIAM C. STADIE, Professor of Research Medicine, The John Herr Musser Department of Research Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pa.

Presentation of the Banting Medal to L. H. NEWBURGH, Professor Emeritus of Clinical Investigation, University of Michigan Medical School, Ann Arbor, Mich.

Response by CECIL STRIKER on behalf of Doctor NEWBURGH

Presentation of citation to MRS. EARL R. HOOVER, Vice President, The Diabetes Association of Greater Cleveland, by EDWIN W. GATES, Chairman, Assembly of Delegates, American Diabetes Association

Address by ALFRED E. EMERSON, Professor of Zoology, University of Chicago, Chicago, Ill., "Social Homeostasis"

SCIENTIFIC SESSION

Sunday, June 10, 9:00 a.m.

HENRY T. RICKETTS, Presiding

The Personality and Intelligence of Diabetics

A. J. KUBANY (by invitation), T. S. DANOWSKI, and C. MOSES, Presbyterian and Children's Hospital, and the Addison H. Gibson Laboratory of the University of Pittsburgh, School of Medicine, Pittsburgh, Pa.

Observations on the Cause and Mechanism of Insulin Resistance During Diabetic Acidosis

JAMES B. FIELD, and DEWITT STETTEN, JR., (by invitation), National Institutes of Health, Bethesda, Md.

Natural Course and Prognosis of Juvenile Diabetes

PRISCILLA WHITE, Tufts College Medical School and Joslin Clinic, Boston, Mass.

The Relative Importance of Duration and Control in the Development of Diabetic Retinopathy

ROBERT C. HARDIN, THEODORE L. JOHNSTON (by invitation), HELEN G. KELLY, M.S., (by invitation), University Hospital and State University of Iowa College of Medicine, Iowa City, Iowa, and ROBERT L. JACKSON, University of Missouri School of Medicine, Columbia, Mo.

Study of Abnormal Carbohydrate Metabolism in Pregnancy

HUGH L. C. WILKERSON, U. S. Public Health Service, Boston, Mass.

Spontaneous Hypoglycemia as a Manifestation of Early Diabetes Mellitus

HOLBROOKE S. SELTZER, STEFAN S. FAJANS and JEROME W. CONN, University Hospital, Ann Arbor, Mich.

PANEL DISCUSSION

Unstable Diabetes

ALEXANDER MARBLE, Moderator, Harvard Medical School and Joslin Clinic, Boston, Mass.

ROBERT L. JACKSON, University of Missouri School of Medicine and University Hospitals, Columbia, Mo.

E. PAUL SHERIDAN, University of Colorado Medical Center and St. Luke's Hospital, Denver, Colo.

GEORGE M. GUEST, University of Cincinnati College of Medicine and Cincinnati Children's Hospital, Cincinnati, Ohio.

GARFIELD G. DUNCAN, Jefferson Medical College, Pennsylvania Hospital and Benjamin Franklin Clinic, Philadelphia, Pa.

SCIENTIFIC SESSION

Sunday, June 10, 2:30 p.m.

FREDERICK W. WILLIAMS, Presiding

On the Mechanism of the Effect of Muscular Work on the Hyperglycemia of Diabetes

RACHMIEL LEVINE (by invitation), M. S. GOLDSTEIN (by invitation), and I. FRITZ (by invitation), Michael Reese Hospital, Chicago, Ill.

PANEL DISCUSSION

Vascular Disease

ARTHUR R. COLWELL, Moderator, Northwestern University Medical School, Chicago, Ill.

BERNARD BECKER, Washington University, School of Medicine, St. Louis, Mo.

PHILIP M. LECOMPTE (by invitation), The Faulkner Hospital, Boston, Mass.

FORREST E. KENDALL (by invitation), Goldwater Memorial Hospital, New York, N. Y.

LOUIS K. ALPERT, George Washington University School of Medicine and Veterans Administration Hospital, Washington, D. C.

Clinical and Pharmacological Effects of N^1-(n-Butylcarbamyl) sulfanilamide (Substance BZ-55) in Diabetes

W. R. KIRTLEY, A. S. RIDOLFO (by invitation), M. A. ROOT, and R. C. ANDERSON (by invitation), Lilly Laboratory for Clinical Research and Lilly Research Laboratories, Indianapolis, Ind.

Studies of the Actions of Oral Antidiabetic Compounds

R. W. COX (by invitation), ELAINE D. HENLEY (by invitation), E. B. FERGUS (by invitation), and ROBERT H. WILLIAMS, University of Washington School of Medicine, Seattle, Wash.

DISCUSSION OF BOTH OF THE ABOVE PAPERS

FREDERICK M. ALLEN, New York Polyclinic Medical School and Hospital, New York, N. Y.

GARFIELD G. DUNCAN, Jefferson Medical College, Pennsylvania Hospital and Benjamin Franklin Clinic, Philadelphia, Pa.

HOWARD F. ROOT, Harvard Medical School and New England Deaconess Hospital, Boston, Mass.

RACHMIEL LEVINE (by invitation), Michael Reese Hospital, Chicago, Ill.

CHARLES H. BEST, University of Toronto Faculty of Medicine, Toronto, Ontario, Canada.

BY TITLE

Xanthoma and Diabetes Mellitus: A Reevaluation of Xanthoma Diabeticorum

DAVID ADLERSBERG, GERALD BRILL (by invitation), CHUN-I WANG (by invitation), and ELAINE T. BOSSAK (by invitation), The Mount Sinai Hospital, New York, N. Y.

A Comparison of the Incidence of Cancer in Nondiabetics and in Diabetics

E. T. BELL, The Medical School, University of Minnesota, Minneapolis, Minn.

The Determination and Significance of Serum Mucoprotein and Mucopolysaccharide in Degenerative Vascular Disease Associated with Diabetes Mellitus

J. M. B. BLOODWORTH, JR., and GEORGE J. HAMWI, Ohio State University College of Medicine, Columbus, Ohio.

The Histopathology of Human and Experimental Retinal Microaneurysms

J. M. B. BLOODWORTH, JR., and GEORGE J. HAMWI, Ohio State University College of Medicine, Columbus, Ohio.

Quantitative Lipoprotein Studies in Diabetic and Other Subjects Using Combined Paper Electrophoretic and Chemical Techniques

FREDERICK R. BROWN, JR., (by invitation), GEORGE D. MICHAELS (by invitation), FUDEKO MARUYAMA (by invitation), and LAURANCE W. KINSELL, with the technical assistance of SADIE SMYRL (by invitation), and JUNE BILISOLY (by invitation), Institute for Metabolic Research, Highland Alameda County Hospital, Oakland, Calif.

Clinical Experience with Ultra-Lente Insulin

M. DAVID DEREN, St. Vincent's Hospital, Bridgeport, Conn., and Yale University School of Medicine, New Haven, Conn.

Clinical Experience with U-2043, Sulfonylurea (Orinase)

HENRY DOLGER, JOHN J. BOOKMAN (by invitation), and ROBERT H. JOELSON, The Mount Sinai Hospital, New York, N. Y.

Metabolic Effects of Oral Hypoglycemic Aryl Sulfonylurea Compounds (BZ-55 and U-2043)

STEFAN S. FAJANS, JEROME W. CONN, LAWRENCE H. LOUIS (by invitation), HOLBROOKE S. SELTZER, ROBERT D. JOHNSON, ROBERT D. GITTLER, ALLEN R. HENNES (by invitation), BERNARDO L. WAJCHENBERG (by invitation), and IRVING P. ACKERMAN (by invitation), University of Michigan Medical School, Ann Arbor, Mich.

Some Observations Which Relate to the Management of Infants Born to Diabetic and "Pre-Diabetic" Mothers

ALFRED E. FISCHER, and RALPH E. MOLOSHOK (by invitation), The Mount Sinai Hospital, New York, N. Y.

Glucagon and Liver Glycogen

PIERO P. FOA, ERMINIO COSTA (by invitation), and GIORGIO GALANSINO (by invitation), The Chicago Medical School, Chicago, Ill.

The Effects of Diets Containing Relatively Large Amounts of Unsaturated Fat Upon Lipid Metabolism in Diabetic Patients

ROGER W. FRISKEY (by invitation), GEORGE D. MICHAELS (by invitation), FUDEKO MARUYAMA (by invitation), and LAURANCE W. KINSELL, with the technical assistance of SADIE SMYRL (by invitation), FLORENCE OLSON (by invitation), and MARJORIE COELHO (by invitation), Institute for Metabolic Research, Highland Alameda County Hospital, Oakland, Calif.

Alteration of Carbohydrate Metabolism in Patients with Cancer

ARVIN S. GLICKSMAN (by invitation), Memorial Hospital and R. W. RAWSON (by invitation), Memorial Hospital and Cornell University Medical College, New York, N. Y.

Evidence That an Oral Hypoglycemic Agent (U-2043) Acts as an Insulin

FREDERICK C. GOETZ, A. SIGRID GILBERTSEN (by invitation), and VALERIE JOSEPHSON, B.S., (by invitation), The Medical School, University of Minnesota, Minneapolis, Minn.

The Distribution of Radioiodinated Glucagon in Rats

ELAINE D. HENLEY (by invitation), ROBERT W. COX (by invitation), H. T. NARAHARA and ROBERT H. WILLIAMS, University of Washington School of Medicine, Seattle, Wash.

Studies on the Interrelationships of the Adrenal Cortex and Diabetes Mellitus. I. Metabolic Effects of ACTH in Unstable Diabetics

JOSEPH L. IZZO, with the assistance of CECILIA KELLNER, B.S., (by invitation), ALFREDA SUSKIE, B.S., (by invitation), ANN EILERS, B.S., (by invitation), and ANGELA RONCONE, B.S., (by invitation), University of Rochester School of Medicine and Dentistry, and Rochester Medical Center, Rochester, N. Y.

Inhibiting Effect of Renal Extract (Tubulin) on Steroid Diabetes

BENJAMIN JABLONS, and ALFONS BUSZA (by invitation), Goldwater Memorial Hospital, New York, N. Y.

Clinical Experiences with 'BZ-55' (N^1-(n-Butylcarbamyl) Sulfanilamide)

CHARLES JOINER (by invitation), Pennsylvania Hospital, and GARFIELD G. DUNCAN, Benjamin Franklin Clinic and Pennsylvania Hospital, Philadelphia, Pa.

Alterations in the Renal Threshold for Sugar by Cortisone and Growth Hormone

THOMAS H. McGAVACK, New York Medical College, New York, N. Y.

The Effects of a Gradually Increased Carbohydrate Load on the Carbohydrate Tolerance of Patients with Diabetes Mellitus

THOMAS H. McGAVACK, New York Medical College, New York, N. Y.

Further Considerations of the Insulin Paradox

RICHARD M. McKEAN, and ROBERT H. HAMBURG (by invitation), Harper Hospital, Detroit, Mich.

The Use of Orinase in the Management of Various Types of Diabetes Mellitus and its Influence on the Pancreatic Content and Peripheral Effect of Glucagon

MAX MILLER, JAMES W. CRAIG (by invitation), JACQUES BERTHET (by invitation), MAYNARD MAKMAN (by invitation), EARL W. SUTHERLAND, JR., (by invitation), SHERWIN J. COOPERSTEIN (by invitation), and MALCOLM S. MACKENZIE (by invitation), Western Reserve University School of Medicine, Cleveland, Ohio.

The Effects of Continuous Fructose Feeding in Diabetic Patients

JOHN A. MOORHOUSE (by invitation), and ROBERT M. KARK (by invitation), Presbyterian Hospital, Cook County Hospital, and University of Illinois Hospitals, Chicago, Ill.

Studies on the Mechanism of Insulin Action

ROBERT L. REEVES, University of Washington School of Medicine and The Mason Clinic, RANDOLPH CLEMENTS (by invitation), The Mason Clinic, and JOSEPH H. CRAMPTON, WILLIAM J. STEENROD and LESTER J. PALMER, University of Washington School of Medicine and The Mason Clinic, Seattle, Wash.

The Effect of Vitamin B_{12} Upon Insulin Requirement in Diabetes Mellitus With and Without Degenerative Complications

LEON S. SMELO, BETTY PENDLETON (by invitation), LEMUEL D. WRIGHT (by invitation), S. CLYDE STRICKLAND (by invitation), and WILLIAM P. BOGER (by invitation), Medical Diagnostic Clinic, Birmingham, Alabama; Norristown State Hospital, Norristown, Pa., and Research Laboratories, Sharp and Dohme, Division of Merck and Company, West Point, Pa.

A Modified Guillotine Amputation. Follow-Up of 50 Diabetics from 1930-1950

BEVERLY CHEW SMITH, New York, N. Y.

Galactose Utilization in Patients with Disturbances of Carbohydrate Metabolism

ALBERT I. WINEGRAD (by invitation), E. RUDOLF FROESCH (by invitation), and ALBERT E. RENOLD, Harvard Medical School and the Peter Bent Brigham Hospital, Boston, Mass.

Changes in the Hypoglycemic Effect of PZI-Insulin Mixtures Through Alterations of *p*H

L. WISLICKI (by invitation), Hebrew University, Hadassah Medical School, Jerusalem, Israel.

The Effects of Parabutamine (N_1-Sulfanilyl-N_2-n-Butylcarbamide) on Human Diabetic Metabolism. 1. Clinical Studies.

JAMES T. WORTHAM, ROSLYN WIENER (by invitation), and WILLIAM H. PERKINS (by invitation), University of Arkansas School of Medicine, Little Rock, Ark.

FIFTH POSTGRADUATE COURSE: Jan. 23-25, 1957

The Fifth Postgraduate Course on Diabetes and Basic Metabolic Problems will be held by the American Diabetes Association Wednesday through Friday, Jan. 23-25, 1957, at the Ohio State Health Center, Columbus, Ohio. The Course is under the direction of George J. Hamwi, M.D.

FOURTH POSTGRADUATE COURSE

The Fourth Postgraduate Course on Diabetes and Basic Metabolic Problems sponsored by the American Diabetes Association was held in Dallas, Texas, Jan. 25-27, 1956, in cooperation with the Southwestern Medical School of the University of Texas, the Dallas Academy of Internal Medicine, and the Dallas Diabetes Association. The Course was developed by the Association's Committee on Professional Education under the Chairmanship of Garfield G. Duncan, M.D., and was directed by Edwin L. Rippy, M.D., Associate Professor of Clinical Medicine, Southwestern Medical School of the University of Texas and Baylor University Hospital, Dallas.

Members of the Local Committee on Arrangements were: Lawrence Cameron, M.D., David W. Carter, Jr., M.D., John S. Chapman, M.D., Leonard J. Flohr, M.D., Jabez Galt, M.D., Arthur Grollman, M.D., E. Russell Hayes, M.D., George M. Jones, M.D., Robert K. Portman, M.D., and Donald W. Seldin, M.D.

The comments of some of those who attended illustrate the success of the Course.

"The general Course is very instructive and im-

pressive. It gives a practical resume of a very important and common disorder."

". . . I thoroughly enjoyed the Course, have learned much, and intend to attend future Courses."

"This was a wonderfully well organized and presented session. I think a remarkaby good balance was attained between subject and presentation geared for the internist with a sound basic knowledge of diabetes and the general practitioner less concerned in his practice with the disease."

"Excellent review and comprehensive subject coverage."

". . . Panel Discussions very good to promote registrant participation. In general an excellent Course, considering the varied background of audience . . ."

"The Course presented a nice balance of clinical, pathological and laboratory work in diabetes. Subjects were well chosen and presentation was on the whole outstanding . . . Dr. Rippy and his Committee did a beautiful job in the organization of the program, both social and scientific."

Physicians in attendance numbered 181. Five of this number have attended all four courses; five have attended three; and twenty-three have attended two courses.

The following is a registration breakdown for the Fourth Postgraduate Course, as well as a comparison with the three previous Courses:

	1956 Dallas	1955 Philadelphia	1954 Rochester	1953 Toronto
Members	82	135	83	93
Membership applications pending	52	23	24	23
Nonmembers	47	18	17	61
Total	181	176	124	177
Part-time registrants		2		
Graduate students		1	*	*
Fellows	2	3	*	*
Residents	10	10	*	*
Interns	4	5	*	*
Medical students	61	11	*	*
Guests	4	6		
Total	81	38		
Grand Total	262	214	124	177
	Additional Data			
Cancellations	12	15	25	5
Applications rejected due to limited facilities			47	92
Attendance at banquet	324	246	208	236

*Graduate students, Fellows, Residents, Interns and Medical Students were not formally registered in 1954 and 1953, and there were a few in attendance.

ADA RESEARCH FELLOWSHIPS

The Committee on Research and Fellowships announces the award of Fellowships to William K. Jenson, M.D., Philadelphia, and John W. Vester, M.D., University of Pennsylvania, Philadelphia. Dr. Jenson will study the potentiation of the action of insulin by the mildly hypoglycemic drugs used in the treatment of hypertension; he will work with Dr. William N. Mann, Head of the Department of Medicine at Guy's Hospital, London, England, Sept. 1, 1956, through Aug. 31, 1957. Dr. Vester will continue his study of oxidative phosphorylation with Dr. William C. Stadie, Head of the Department of Research Medicine at the Hospital of the University of Pennsylvania, July 1, 1956, through June 30, 1957.

Plans are being made to award at least one Fellowship for the academic year 1957-58. Requests for application forms and other inquiries should be addressed to the Association's Executive Director, Mr. J. Richard Connelly, who will forward the information to the Committee on Research and Fellowships.

FACTS BOOKLET AVAILABLE

The American Diabetes Association announces the publication of *Facts about Diabetes*, a 32-page three-color booklet especially prepared for the information of the general public and the new diabetic. Single copies will be sold for 25c each. Bulk sales to Affiliate Associations will be at the special price of $18.00 per hundred, which includes shipping charges. Bulk sales to other organizations and individuals will be made at $20.00 per hundred, which also includes shipping costs.

Facts about Diabetes is full of valuable information about the ailment. Written by a well-known science writer under the direction of the Committee on Detection and Education (through its Steering Committee), the text has been approved by the Executive Committee. It will be a valuable addition to the reception room library of every physician who treats diabetics.

NEW COMMITTEE ON SCIENTIFIC AWARDS

A special Committee on Scientific Awards has been established by the American Diabetes Association, which supersedes the Subcommittee on Awards of the Editorial Board of DIABETES. Members of the new Committee include E. Perry McCullagh, M.D., Chairman, Irving Graef, M.D., Francis D. W. Lukens, M.D., John A. Reed, M.D., and Randall G. Sprague, M.D. Establishment of the new Committee was made by the Council upon recommendation of the Executive Committee at the Interim Meeting, Jan. 28-29, 1956, in Dallas.

FOURTH MEDICAL STUDENT-INTERN ESSAY CONTEST

The fourth Medical Student-Intern Essay Contest, open to medical students, interns and physicians within two years after their graduation from medical school, is sponsored by the American Diabetes Association. Contestants may choose any subject relating to diabetes and basic metabolic problems. Association members are requested to encourage medical students and interns in their schools and hospitals to enter.

A prize of $250 to the author or authors of the best paper reporting original work, whether laboratory investigation or clinical observation, has been made possible once again by the kindness of the St. Louis Diabetes Association. An award of $50 for the best review article or case report will also be included in this year's prizes.

Manuscripts, typewritten with double-spacing, should be submitted by May 10, 1956, to the Committee on Scientific Awards, American Diabetes Association, 1 East 45th St., New York 17, N. Y. The essays will be reviewed by members of the Committee who, in selecting the best papers, will consider both the value of the material and the method of presentation.

DIABETES WEEK, 1956

The week of November 11-17 will be observed as Diabetes Week this year. The Council upon recommendation of the Executive Committee at the Interim Meeting, Jan. 28-29, 1956, in Dallas, officially selected the week preceding Thanksgiving as Diabetes Week for this and succeeding years.

GLYCOSURIA AND DIABETES

A limited number of copies of *Studies Concerning Glycosuria and Diabetes,* by Frederick M. Allen, M.D., published by the Harvard University Press in 1913, are still available without charge through the courtesy of a grant from Eli Lilly and Company.

The book describes the production of diabetes by partial pancreatectomy, the first experimental production of hydropic degeneration of pancreatic islands and other early experimentations.

Preference will be given first to libraries and then to interested individuals, in view of the importance of the book for historic and reference purposes. Requests for the book should be sent to the National Office of the American Diabetes Association.

STUDENT SUBSCRIPTION RATES

As previously announced, medical students, interns and residents may subscribe to DIABETES at $4.50 per year, half of the regular subscription rate.

NEW MEMBERS

ACTIVE

The following were elected as of March 1 and April 1, 1956:

Alabama	
Wright, Ralph D.	Mobile
California	
Clark, William H.	Palo Alto
Kiely, James P.	La Jolla
Lipkis, Maurice L.	Los Angeles
McNiece, Kenneth J.	Santa Barbara
Colorado	
Robertson, Howard T.	Denver
Thompson, Lloyd L.	Denver
Florida	
Roberts, Hyman J.	West Palm Beach
Georgia	
Moncrief, William M.	Atlanta
Illinois	
Colwell, Arthur R., Jr.	Wilmette
Indiana	
Baxter, Neal E.	Bloomington
Burkhardt, Boyd A.	Tipton
Heminway, Norman L.	Elkhart
Root, Mary A.	Indianapolis
Ziss, Robert C.	Evansville
Kansas	
Swan, M. M.	Great Bend
Westfall, George A., Jr.	Halstead
Wood, Gary B.	Wichita
Kentucky	
Harvey, Daryl P.	Glasgow
Louisiana	
Joseph, Cheney C.	Baton Rouge
Kelly, James D.	Monroe
Locke, William	New Orleans
Marshall, Thomas E.	Shreveport
Minnesota	
Lundsten, Lloyd R.	Rochester
Nebraska	
Charlton, George P.	Hastings
New Hampshire	
Rainie, Robert C.	Concord
New Jersey	
Rogers, John G.	Riverton
New York	
Fischl, Jacques R.	New York
Marton, Richard S.	New York
Paley, Karl R.	New York
Vorhaus, Louis J., II	New York
Ohio	
Borer, Raymond J.	Toledo
Dumm, Robert M.	Kent

Hiss, Frederick W.	Toledo
Morris, Nelson D.	Toledo
Sag, William E.	Alliance
Oklahoma	
Goen, Rayburne W.	Tulsa
Pennsylvania	
Cohen, Norman	Pittsburgh
Emerson, Howard B.	Tarentum
Knox, Kenneth R.	Philadelphia
Slayton, Robert E.	Philadelphia
Troncelliti, Alfred E.	Ardmore
Wilt, Harold L.	Brownsville
Texas	
Bassel, Paul M.	Temple
Boyd, Virginia H.	Abilene
Burrows, John B.	Houston
Hanson, Hugh H.	Houston
Kahn, Samuel H.	Dallas
Kilgore, Donald G.	Dallas
McDonald, Donald H.	Abilene
Medford, Ulen G.	Lufkin
Robbins, Leonard R.	Houston
Schulze, Victor E.	San Angelo
Spikes, George A.	Hallettsville
Starr, Pete J.	Dallas
Veatch, Everett P.	Pasadena
Veninga, Frederick W.	Dallas
Utah	
Evans, Burtis R.	Salt Lake City
Washington	
Welsh, George W., III	Seattle
Other Countries	
Canada	
Gold, Allen	Montreal
England	
Goldstein, Jacob	Dartford, Kent

NEWS OF AFFILIATE ASSOCIATIONS

THE CHICAGO DIABETES ASSOCIATION will sponsor a symposium on the "Clinical and Public Health Aspects of Diabetes" on May 11-12. The Chicago Board of Health, the Illinois Department of Public Health and the U. S. Public Health Service are co-sponsors. "Degenerative Complications of Diabetes," "The Juvenile Diabetic," and "Pregnancy in Diabetes" are among the topics scheduled for discussion. There will also be a demonstration of the use of testing equipment for screening programs. Faculty members include Henry T. Ricketts, M.D., Professor of Medicine, University of Chicago School of Medicine; Arthur R. Colwell, M.D., Professor and Chairman of the Department of Medicine, Northwestern University School of Medicine; Arnold B. Kurlander, M.D., Medical Director, Chief, Chronic Disease Program, Division of Special Health Services, U. S. Public Health Service; and Hugh L. C. Wilkerson, M.D., Medical Director of Diabetes Field Research and Training Unit, U. S. Public Health Service, Boston.

The course has been approved by the Illinois Academy of General Practice for Category II (informal) postgraduate credit. No fees for registration or attendance will be charged. Physicians and public health officers in Illinois and neighboring states are invited to attend. Attendance at the conference may be arranged by writing to: Chicago Diabetes Association, 5 South Wabash Ave., Chicago 3, Ill.

THE TEXAS DIABETES ASSOCIATION will present the following morning program at an all-day meeting to be held in Galveston on April 22: "Observations on Variations in the Dietary Program in the Treatment of Indigent Diabetics," by George Perdue, M.D., H. T. Engelhardt, M.D., and Miss Marguerite Coronado; "Sickle Cell Trait in Negro Diabetics," by Carlos Speck, M.D.; "Hypoglycemia in a Child, Treated with ACTH, Glucagon and Pancreatectomy," by William Daeschner, M.D., and George Salmon, M.D.; "Coma and Psychosis Following Possible Insulin Sensitivity," by Nathan Cotlar, M.D.; and "Diabetic Coma, Physiologic and Therapeutic Aspects," by F. R. Keating, Jr., M.D., Rochester, Minnesota.

The afternoon program will begin at 12:30 p.m., with a luncheon and panel "Management of the Diabetic in Stress," by F. R. Keating, Jr., M.D., James A. Greene, M.D., Raymond Gregory, M.D., and Edwin L. Rippy, M.D., with Mavis P. Kelsey, M.D., as Moderator, after which the following papers will be given: "Psychological and Psychiatric Problems in the Management of the Child with Diabetes," by Orie Forbis, M.D.; "Diabetes in Pregnancy," by Robert Johnston, M.D., and Doye R. Bridges, M.D.; "Sheehan's Syndrome in a Diabetic Occurring Antepartum," by Donald Paton, M.D., and Dan M. Queen, M.D.; "Results of Treatment of Diabetic Neuropathy with Vitamin B_{12}," by John E. Johnson, Jr., M.D.; and "Addison's Disease Developing in a Diabetic," by John J. Sloan, M.D., and John W. Chriss, M.D.

NEWS NOTES

SYMPOSIUM ON VITAMIN METABOLISM

A Symposium on Vitamin Metabolism was held in New York City on March 6, in conjunction with the Eleventh Annual Meeting of The National Vitamin Foundation, Inc. The Symposium, presented in cooperation with the University of Texas, was attended by 300

scientists from medical centers, laboratories and scientific institutions in the United States. Russell M. Wilder, M.D., Rochester, Minnesota, is President of The National Vitamin Foundation.

PRIZE WINNER ANNOUNCEMENT

Le Diabete, with editorial offices at 21, rue Saint-Fiacre, Paris, will announce in May the winner of a prize of 50,000 francs for a paper dealing with diabetes and its problems. The contest closed January 31.

NUTRITION LEAFLETS

The American Dietetic Association announces the availability of the following leaflets: *The Best of Health to You* (nutrition information for adults), *Forget Birthdays—Enjoy Good Eating* (nutrition for the senior citizen), *More, Please* (normal nutrition and dental health for children), and *Selected List of References on National Food Patterns and Recipes* (fourteen mimeographed pages of book titles). These inexpensive leaflets on the subject of nutrition may be ordered from The American Dietetic Association, 620 North Michigan Ave., Chicago 11, Ill.

PERSONALS

GARFIELD G. DUNCAN, M.D., will be Director of "Some Recent Developments in Principles and Practice of Modern Internal Medicine," a postgraduate course arranged by The American College of Physicians. The course will be held May 14-18 at the Pennsylvania Hospital in Philadelphia.

ROBERT F. LOEB, M.D., was Co-director of "Selected Subjects in Internal Medicine," also arranged by The American College of Physicians, and held March 12-16 at Columbia-Presbyterian Medical Center in New York.

HENRY B. MULHOLLAND, M.D., immediate past President of the American Diabetes Association, will participate in the *March of Medicine* television program, "The Lengthening Span," on April 1. As Chairman of the Geriatric Committee of the American Medical Association, Dr. Mulholland will discuss how the medical profession can help our senior citizens to live a more vigorous and happy life, not just one of survival.

OBITUARY

ADOLPH SACHS, M.D., Omaha, Nebraska, died May 2, 1955, at the age of 69. Born in Cheyenne, Wyoming, Dec. 31, 1885, Dr. Sachs was graduated from the College of Medicine of Creighton University in 1907. Following his internship at St. Joseph's Hospital in Omaha, Dr. Sachs pursued postgraduate study at the University of Berlin, University of Vienna, and in London, Boston and New York City. He returned to Omaha in 1909 to engage in the practice of internal medicine.

Dr. Sachs was Professor of Medicine at Creighton Medical College and a member of the attending staff of St. Joseph's Hospital, becoming head of the Department of Medicine in both institutions. He was a member of the staff of St. Catherine's Hospital, Doctor's Hospital, The Nebraska Methodist Hospital, and Immanuel Hospital; Director of the Eastern Division of the Union Pacific Railroad Medical Department; and for the past five years Special Consultant on the staff of the president of this railroad. A member of the American Diabetes Association since 1941, Dr. Sachs was a diplomate of the American Board of Internal Medicine, a member of the American College of Physicians, of which he served as Governor for twelve years, the Central Society for Clinical Research, the American Gastro-Enterological Association, the International Society of Gastro-Enterology, United States Committee of the World Medical Association, American Association for the Advancement of Science and the Association for the Study of Internal Secretions.

In 1948, Dr. Sachs received from Pope Pius the Twelfth the citation of Knight Commander with Star, of the Order of St. Gregory the Great, "for his work of Charity, Humility, Wisdom and Loyalty." He was the fourth non-Catholic ever to receive such an honor.

He is survived by his wife and daughter.